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ORIGINAL ARTICLE

Aetiology of Cytopenias in Children Admitted to a Tertiary Care Hospital

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ABSTRACT

Objective: To determine the aetiology of cytopenias (pancytopenia and bicytopenia) in children and to assess their relationship with demographic factors, clinical manifestations and disease outcome.

Patients and Methods: This cross-sectional study was carried out at the Children's Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad from January 2015 to June 2016. Total of 154 children between the ages of 2 months to 12 years presenting with bicytopenia or pancytopenia, at the time of admission were enrolled in the study. Patients with known causes of cytopenias and those with chronic illnesses and on long term medications like chemotherapy or immunosuppressant were excluded.

Results: The causes of cytopenia in order of frequency were Acute Leukemia (25%), Aplastic Anemia (20%), Enteric fever (19%) and megaloblastic anemia (11%).Out of 38 Acute Leukemia patients, 61 % presented with bicytopenia and 39% with pancytopenia, whereas out of the 31 patients of Aplastic anemia, 29 (94%) presented with pancytopenia. Among 19 patients of enteric fever, 13(68%) had bicytopenia and 6 (32%) patients presented with pancytopenia. Total patients of megaloblastic anemia were 17 out of which 10 (59%) presented with bicytopenia and 7 (41%) with pancytopenia. All patients of Idiopathic Thrombocytopenic purpura ITP (N=9), Osteopetrosis (N=3), Amegakaryocytic thrombocytopenia (N=2), and Myelodysplastic syndrome (N=2) presented with bicytopenia.

Conclusion: The most common cause of cytopenia was found to be acute leukemia followed by aplastic anemia, enteric fever and megaloblastic anemia

Keywords: Children, Bicytopenia, Pancytopenia

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing
[2] Interpretation and discussion
[3] Data analysis, interpretation and manuscript writing, [4, 5] Active participation in data collection

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Article info.
Received: April 19, 2017
Accepted: May 23, 2017

Cite this article: *Waris R, Shahid G, Khalid ST, Riaz A, Rehman A. Aetiology of Cytopenias in Children Admitted to a Tertiary Care Hospital JIMDC. 2017; 6(2):104-109.*

Funding Source: *Nil*
Conflict of Interest: *Nil*

Introduction

Peripheral cytopenia is defined as reduction in any one of the cellular elements of blood i.e., red blood cells, white blood cells or platelets. Cytopenia is taken as Hemoglobin <10 gm/dl and/or TLC <4000 cmm and/or Platelets < $100x10^6$/l ([i]). Bicytopenia (BC) is reduction in any of the two cell lines and pancytopenia (PC) is reduction in all the three cell lines.[1,2] The etiology of cytopenias varies widely in children ranging from transient marrow suppression to marrow infiltrations by life threatening malignancies.[1] The underlying pathogenic mechanisms of cytopenias are variable and include decrease in hematopoietic cell production, marrow replacement by abnormal cells, suppression of marrow growth and differentiation, ineffective hematopoiesis with cell death, defective cell

formation which are removed from the circulation, antibody mediated destruction of cells or trapping of cells in hyperplastic and overactive reticuloendothelial system.[1-3] Other causes of suppressed hematopoiesis are nutritional deficiencies as observed in vitamin B12, folate and iron deficiency.[1,2] Irrespective of aetiology, patients with cytopenias may present with fever, pallor, bleeding, hepatosplenomegaly etc. However, outcomes of cytopenias vary widely depending on the cause, from being a mild transient illness to a serious life-threatening disease. To start appropriate treatment timely, knowledge of various diseases underlying cytopenic process is essential.[3] Different frequencies of causes of PC have been reported in a number of studies.[3,5] This study was conducted with the aim to assess the variable causes of bicytopenia/pancytopenia in the pediatric age group in our setup and to determine their association with various demographic factors, clinical manifestations and disease outcome.

Patients and Methods

This cross-sectional study was carried out at Children's Hospital, PIMS from 1st Jan 2015 to 30th June 2016. A total of 154 children between 2 months-12 years, presenting and being admitted for the first time with bicytopenia/pancytopenia on complete blood counts were included in the study. Cytopenia was defined as Hemoglobin <10 gm/dl and/or TLC <4000 cmm and/or Platelets < $100x10^6$/l.[2] Patients on long term therapy with immunosuppressant, anticonvulsants, chemotherapeutic agents or any other drugs being taken for any chronic illness were excluded from the study as were children who had already been worked up for cytopenias previously. Detailed history was taken and a thorough physical examination was done on all the study patients at the time of presentation. Hematological profile included hemoglobin, red cell indices, total and differential leukocyte count, platelet count, and peripheral blood smear morphology. ICT MP and Typhidot were also performed on selected cases where there was a clinical suspicion of malaria or typhoid fever. Blood counts were done on automated hematology analyzer and were confirmed by peripheral blood smear examination. Bone marrow aspirate and trephine biopsy were carried out as per clinical indication.

Results

Our sample size of 154 represents 5.58% of the total admissions in general pediatric ward. Out of these 154 patients, 85(55%) were presented with BC whereas 69(45%) with PC. The mean age of the study population was 5.7 years ±3.6 (range 2 months-12years) with a male to female ratio of 1.5:1. As regards the Geographical distribution (GD) of our patients, most of the patients were from Punjab province (N=50 [32.4%]) and twin cities of Rawalpindi/ Islamabad (N=43 [27.9%]). Rest of the patients were from Azad Jammu Kashmir (AJK) and Khyber-Pakhtunkhwa (KPK) province. The geographical distribution of the study population is represented in Figure.1.

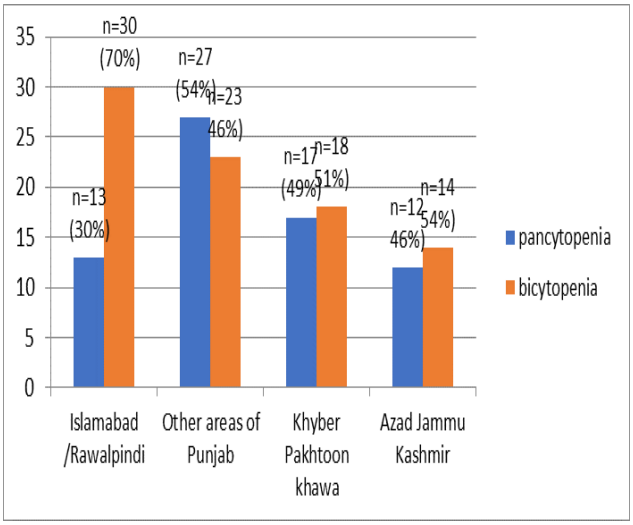

Figure 1: Geographical distribution of patients with Pancytopenia/ Bicytopenia

If we look at the aetiology of cytopenias according to the GD, out of 43 patients from Rawalpindi/ Islamabad; 12 (28 %) were diagnosed with enteric fever and 11 (23%) with ALL, followed by Megaloblastic Anemia and Aplastic Anemia 5 (12%) each. Most common diagnosis in patients from other areas of Punjab was ALL 13 (26%), followed by Megaloblastic Anemia and Aplastic Anemia 20% each, and enteric fever 8%. There were 11 cases of Leishmaniasis, and all of them were from AJK, and these represent 41% of all cases from AJK. Other common causes from AJK were Aplastic anemia 19%, ITP 15% and ALL 7%. Patients from KPK were diagnosed as ALL (37%) followed by Aplastic Anemia (31%).

Overall, the causes of cytopenia in order of frequency were ALL (25%), Aplastic Anemia (20%), Enteric fever (19%) and Megaloblastic anemia (11%). Other less frequent causes included Leishmaniasis, Malaria, ITP, unspecified infections, Osteopetrosis, HLH, Autoimmune hemolytic anemia, Amegakaryocytic thrombocytopenia, Chediak-Higashi syndrome, and Myelodysplastic syndrome- details shown in table 1.

The age distribution of the various aetiologies (Table 1) were as follows; ALL- mean age of 5.2 ± 2.8 yrs (range 1-11 yrs), Aplastic Anemia- mean age of 9.7 ±2.0 (range 4-12 yrs), Enteric fever mean age of 6.2 ±3.7 (range 1-12 yrs) and Megaloblastic anemia mean age 3.9±3.8,(range 1-12 yrs).

The most common cause of bicytopenia was Acute Leukemia (27%) and of pancytopenia was Aplastic

Table 1: Etiological profile according to age group

Etiological Profile	Age group			Total No. (%)	Mean age ±SD (Range)
	2 mon -5 yrs	>5-10 yrs	>10-12 Yrs		
Acute Leukemia (AL)	25	10	3	38 (25)	5.2±2.8 (1-11)
Aplastic Anemia	1	14	16	31 (20)	9.7±2.0 (4-12)
Enteric	7	9	3	19 (12)	6.2±3.7 (1-12)
Megaloblastic anemia	12	3	2	17 (11)	3.9±3.8 (1-12)
Leishmaniasis	9	2	0	11 (7)	2.8±2.6 (1-9)
Malaria	5	4	1	10 (6)	5.1±3.4 (0.2-11)
Immune Thrombocytopenic purpura (ITP)	6	1	2	9 (6)	5.1±3.2 (1-11)
Infection related changes	4	1	0	5 (3)	2.9±1.9 (1-6)
Osteopetrosis	2	1	0	3 (2)	2.9±3.5 (0.6-7)
Hemophagocytic Lymphohistiocytosis (HLH)	2	1	0	3 (2)	3.0±4.3 (0.3-8)
Autoimmune hemolytic anemia	2	1	0	3 (2)	3.5±2.8 (1-5)
Amegakaryocytic thrombocytopenia	2	0	0	2 (1)	3.0±2.8 (1-5)
Chédiak–Higashi syndrome	0	1	0	1 (1)	7
Myelodysplastic syndrome	1	1	0	2 (1)	5±2.8 (3-7)
Total	78(51)	49 (32)	27 (18)	154 (100)	

Table 2: Etiological profile of Children presented with Bicytopenia and Pancytopenia

Etiological Profile	Cytopenia		Total
	Pancytopenia	bicytopenia	
Acute Leukemia (AL)	15 (22%)	23(27%)	38
Aplastic Anemia	29(42%)	2(2%)	31
Enteric	6(9%)	13(15%)	19
Megaloblastic anemia	7(10%)	10(12%)	17
Leishmaniasis	5(7%)	6(7%)	11
Malaria	1(1%)	9(11%)	10
Immune Thrombocytopenic purpura (ITP)	0(0%)	9(11%)	9
infection related changes	2(3%)	3(4%)	5
Osteopetrosis	0(0%)	3(4%)	3
Hemophagocytic Lymphohistiocytosis (HLH)	2(3%)	1(1%)	3
autoimmune hemolytic anemia	1(1%)	2(2%)	3
Amegakaryocytic thrombocytopenia	0(0%)	2(2%)	2
Chédiak–Higashi syndrome	1(1%)	0(0%)	1
Myelodysplastic syndrome	0(0%)	2(2%)	2
Total	69	85	154

Table 3: Summary of studies on etiological profile of patients presenting with cytopenia						
Author	**Year**	**Place**	**Study Population**	**Number of Cases**	**Duration of study**	**Most common causes**
Memon et al.[12]	2008	Pakistan (Jamshoro)	Children	230	17 months	Aplastic anemia 23.9%, Megaloblastic anemia 13.04%,Leukemia 13.05%
Shafi.et al.[15]	2012	Pakistan (Lahore)	Children	279	15 months	Acute leukemia 32.2%, Aplastic anemia 30.8%, Megaloblastic anemia 13.2%
Jan AZ et al.[5]	2013	Pakistan (Peshawar)	Children	205	72 months	Aplastic anemia 28.3%, Leukemia 23.9%, Megaloblastic anemia 19.5%,
Sharif et al.[15]	2014	Pakistan (Rawalpindi)	Children	105	12 months	Megaloblastic anemia 41.9%, Infective etiology 19%, Aplastic anemia 13.3%, Acute leukemia 10.5%
Arshad et al.[19]	2016	Pakistan (Faisalabad)	Children and Adults	330	12 months	Aplastic anemia 37.5%, Infections/septicemia 25%, Myelodysplastic syn 12.5%, VL 12.5%
Present Study	2017	Pakistan (Islamabad)	Children	153	18 months	Acute leukemia 25%, Aplastic Anemia 20%, Enteric Fever 19%, Megaloblastic Anemia 11%.
Al- Awadi et al.[4]	2009	Iraq (Hilla)	Children and Adults	74	15 months	Acute leukemia 32.4%, aplastic anemia 24.3%, kalaazar 10.8%
Pine M et al.[18]	2010	United states	Children	64	72 months	Infections 64%,hematologic causes 28%, miscellaneous 8%
Naseem S etal.[3]	2011	India (Chandigarh)	Children	571	24 months	Aplastic anemia 33.8%, acute leukemia 26.6% , megaloblastic anemia 13.7
Pathak R et al.[20]	2012	Nepal (khatmandu)	Children and Adults	503	12 months	Hypoplastic anemia 42.1%, megaloblastic anemia 11.7%, acute leukemia 8.8%
Bae MH et al.[21]	2015	Korea	Children and Adults	640 adults/ 261 children	60 months	Acute leukemia 45.8%,Aplastic anemia 27.3%, Hemophagocytic Lympho Histiocytosis 18.8%
Dobey SRK et al.[16]	2016	India (khanpur UP)	Children	170	20 months	Megaloblastic anemia 47%, aplastic anemia 25.8%, leukemia 17.6%
Singh G et al.[22]	2016	India (Rajhastan)	Children	153	12 months	Severe acute malnutrition 27.3%, leukemia 18.2%, dengue and thalassemia with hypersplenism 9.1%

Anemia (42%).Details of other cause of PC and BC are shown in (Table 2). Lymphadenopathy (14%). Patients with BC presented Comparison of different national and international studies on the etiology of cytopenias is represented in table 3.

Discussion

Cytopenias are fairly common hematologic abnormalities encountered in clinical practice.[5-9] Etiology is highly variable with prognosis varying from a mild transient ailment to a severe life-threatening illness.[8-10] Frequencies of causes of pancytopenia have been reported in a number of studies.[3-5] Early and appropriate investigations and management has a significant effect on the disease course. In this study, there was a predominance of males with the ratio being 1.48:1. Several studies have cited a similar male predominance.[5-14] The reason could be due to social/cultural taboos in our society making health care facilities more readily available to male as compared to females leading to increased male presentation in the hospitals especially in rural areas. About 50.6% of our study patients were less than 5yrs of age. Sharif M et al showed a somewhat greater number (61%) of under 5-year-old children.[13] Looking at the age distribution in

context of different aetiologies of pancytopenia, only aplastic anemia was almost exclusively diagnosed in children more than 4 years of age whereas almost all of the rest of the causes were more common in under 5-year-old children.[3]

The most common cause of cytopenia in our study was Acute Leukemia (25%), followed by aplastic anemia (20%), enteric fever (12%) and Megaloblastic Anemia (11%).These results are somewhat similar to a study by Khan FH et al, who reported ALL (32.2%) as the most common cause of pancytopenia closely followed by Aplastic Anemia (30.8%) and Megaloblastic Anemia (13.2%).[15] However, majority studies have reported Megaloblastic Anemia and Aplastic Anemia as the most common causes of cytopenias.[5, 11] Likely explanation is that our hospital is the largest public-sector tertiary care hospital in the area with a well-established, specialized pediatric oncology unit and therefore receives a number of referrals of suspected malignancies from neighboring areas like KPK, AJK, and other parts of Punjab. Certain other studies have cited megaloblastic anemia as being the most common aetiology.[16,17] A study conducted at the twin city of Rawalpindi/Islamabad showed a very high number of patients with Megaloblastic anemia (42%) followed by infections 19%, Aplastic anemia 18.3%, ALL 10.5% and ITP 5.7 %.[13] The reason for megaloblastic anemia being the most common cause of cytopenia in their study may be probably because of the fact that their study comprised of a very large number (71%) of patients having malnutrition and therefore frequency of Vit.B12 and folic acid deficiency is understandably high. Even then, the most common cause for pancytopenia is megaloblastic anemia but it is under-reported because most of the patients do not get their B12 and folate levels done. As regards infection is concerned infection rate was similar to other studies; we found enteric fever in 17%, malaria in 6% and visceral leishmaniasis in 7%, infection related changes 3%. There are hardly any studies on the subject from the developed countries. Pine et al in their five-year review focused on children presenting with pancytopenia at children's hospital in the United State.[18] Their selection criteria however, was different as they excluded children with malignancies and their age range was also different as they included children from 2 months and upto 18 years of age. They found infections as the most common cause (64%) followed by hematologic causes (28%). In our study 33% of patients with infections presented with cytopenia(s). Not many studies have determined the aetiology of PC and BC separately. In our study, acute leukemia was the most common cause of BC whereas aplastic anemia was the most common diagnosis in those who presented with PC. Similar results were shown by a study in India.

The causes of PC/BC may vary in different patients and in diverse areas of the world. Variations in the frequency of various diagnostic entities have been attributed to differences in patient selection criteria, genetic differences and geographical distribution of the study population. Knowing the etiologies in our own setup helps in the better evaluation and prompt management of patients.

Conclusion

The most common cause of cytopenia was found to be Acute Leukemia followed by Aplastic Anemia, Enteric fever and megaloblastic anemia in a tertiary care hospital setting with a well-established pediatric oncology setup.

References

1. Bates I, Bain BJ. Approach to diagnosis and classification of blood diseases. Dacie and Lewis Practical Hematology. 10th ed. Philadelphia: Churchill Livingstone; 2006.p. 609-24.
2. Raja S, Suman FR, Scott JX, Latha MS, Rajenderan A, Ethican A. Pancytopenia – (?) An obstacle in the diagnosis and outcome of pediatric acute lymphoblastic leukemia. South Asian J Cancer. 2015; 4(2):68–71.
3. Naseem S, Verma N, Das R, Ahluwalia J. Pediatric patients with Bycytopenia/Pancytopenia: Review of etiologies and clinic hematological profile at a tertiary center. Indian J patholMicrobiol 2011; 54(1):75-80
4. Al–Awadi NB, Al-Awad AS, Al-yasiri HH. Patterns of Pancytopenia According to the Cause in Babylon. Medicine (JIACM). 2014; 6(4):434-440.
5. Jan AZ, Zahid B, Gul Z. Pancytopenia in children: A 6 year spectrum of patients admitted to pediatric department of Rehman Medical Institute Peshawar. Pak J Med Sci. 2013; 29(5):1153-1157
6. Makheja KD, Maheshwari BK, Arain S, Kumar S. The common causes leading to pancytopenia in patients presenting to tertiary care hospitals. Pak J Med Sci. 2013; 29(5):1108.

7. Erlacher M, Strahm B. Missing Cells: Pathophysiology, Diagnosis, and Management of (Pan) Cytopenia in Childhood. Front Pediatr. 2015; 3.
8. Azaad MA, Li Y, Zhang Q, Wang H. Detection of pancytopenia associated with clinical manifestation and their final diagnosis. Open J Blood Dis. 2015. 24; 5(3):17-30.
9. Jella R, Jella V. Clinico-hematological analysis of pancytopenia. International Journal of Advances in Medicine. 2017.2; 3(2):176–9.
10. Khan A, Aqeel M, Khan TA, Munir A. Pattern of hematological diseases in hospitalized paeditric patients based on bone marrow examination. Journal of Postgraduate Medical Institute (Peshawar-Pakistan). 2011; 22(3).
11. Gul Z, Ahmed S, Jan AZ. Spectrum of hematological diseases in Pediatric Patients presenting with Anemia based on bone marrow examination. Gomal Journal of Medicine Sciences. 2014; 12(2):60-3.
12. Memon S, Shaikh S, Nizamani A A. Eitiological spectrum of pancytopeniabased on bone marrow examination in children. JColl Physicians Surg Pak. 2008; 18(3):163-167
13. Sharif M, Masood N, ul Haq MZ, Dodhy MA, Muhammad R. Etiological spectrum of pancytopenia/bicytopenia in children 2 months to 12 years of age. Journal of Rawalpindi Medical College (JRMC). 2014; 18(1):61-4.
14. Chhabra A, Chander V, Patel A. Clinico-aetiological profile of pancytopenia in paediatric practice. J Indian Acad Clin Med. 2012; 13:282-5.
15. Khan FS, Hasan RF. Bone marrow examination of pancytopenic children. JPMA-Journal of the Pakistan Medical Association. 2012; 62(7):660.
16. Dobey SR, Patel SK, Ary AK, Singh RP. Clinico-etiological spectrum of pancytopenia in hospitalized children.Int J Contemp Pediatr.2016;3(1):169-172
17. Reddy GP, Rao KV. Clinical features and risk factors of pancytopenia: a study in a tertiary care hospital. International Journal of Advances in Medicine. 2016;3(1):68-72.
18. Pine M, Walter AW. Pancytopenia in hospitalized children: a five-year review. Journal of pediatric hematology/oncology. 2010; 32(5):192-4.
19. Arshad U, Latif RK, Ahmad SQ, Imran MM, Khan F, Jamal S. Clinical and Aetiological Spectrum of Pancytopenia in a Tertiary Care Hospital. Pakistan Armed Forces Medical Journal. 2016; 66(3):323-7.
20. Pathak R, Jha A, Sayami G. Evaluation of bone marrow in patients with pancytopenia. Journal of Pathology of Nepal. 2012 vol.2, 265-271
21. Bae MH, Cho YU, Kim B et al. Pancytopenia or bicytoppenia in a Korean tertiary care center; Etiological profile based on bone marrow examination and suggestion for diagnostic approach. Blood Journal 2015;126(23):5610
22. Singh G, Agrawal DK, Agrawal R. Etiological profile of childhood pancytopenia with special reference to non-malignant presentation. Int J Med Res Prof. 2016;2(2):204-08