Original Article

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Clinico-aetiological and Demographic Profile of Pancytopenia among Children in a Tertiary Care Hospital of Northern Part of West Bengal- A Cross-sectional Study

Paediatrics Section

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ABSTRACT

Introduction: Pancytopenia is a trio of results caused by numerous medical conditions in which all blood cell lineages, such as leukocytes, erythrocytes, and platelets, are diminished in blood. Causes of pancytopenia seem to vary widely in different country and also in different regions within a country. Knowing common cause and common presentation of pancytopenia is of immense importance to determine the diagnosis, especially in resource-constraint areas.

Aim: To assess the aetiology, clinical profile of pancytopenia in a tertiary hospital in northern part of West Bengal.

Materials and Methods: This hospital-based, cross-sectional, study was conducted in North Bengal Medical College and Hospital, Sushrutanagar, West Bengal, India, from July 2012 to June 2013. Patients having pancytopenia, on primary haematological investigation, admitted in the Paediatric Department of the hospital were included in the study. Patients already on definitive treatment for disease causing pancytopenia like kala-azar, leukaemia were excluded from the study. A physical examination was performed after obtaining a relevant clinical history, followed by a full blood count, including Peripheral Blood Smear (PBS) examination, and appropriate biochemical assays. An aspiration and evaluation of the bone marrow was performed. Statistical Package for Social Sciences (SPSS) Version 16.0 for windows (SPSS 16) was used.

Results: There were 50 children, and the mean age of presentation was 7.3 years. Females constituted 52% and males were 48%. Aplastic anaemia was noted in 44% cases, 30% cases were diagnosed as megaloblastic anaemia, kala-azar in 18%, Acute Lymphoblastic Leukaemia (ALL) in 6% and Idiopathic Thrombocytopenic Purpura (ITP) in 2%, respectively. Mean age of presentation in aplastic anaemia was 7.6 years, while that in megaloblastic anaemia was 6.9 years. Female predominance was seen in both aplastic anaemia (59%) and megaloblastic anaemia (60%), while male preponderance was seen in ALL (66%). Generalised weakness was the most prevalent presenting symptom (100%) followed by fever (80%). Pallor (100%) was the most prevalent presenting sign, followed by glossitis (30%), which is commonly ignored.

Conclusion: Though aplastic anaemia is an important cause of pancytopenia, treatable causes like megaloblastic anaemia, kala-azar should always be looked for as other possible aetiologies for pancytopenia.

Keywords: Aplastic anaemia, Megaloblastic anaemia, Pallor

INTRODUCTION

Pancytopenia is a common clinico-haematological condition seen in day-to-day clinical practice. It's described as a drop in the number of all three produced blood constituents (red blood cells, white blood cells, and platelets) below the normal reference range [1]. It is characterised by the presence of anaemia, leucopenia, and thrombocytopenia all at the same time. Patients with pancytopenia have a variety of clinical signs and symptoms. Pallor, malaise, and other symptoms such as palpitation and dyspnea are common in anaemic patients. A patient with thrombocytopenia has bruises, gum bleeding, and petechiae, whereas a patient with leucopenia has a history of recurrent infections. As a result, people with pancytopenia may exhibit any of the symptoms listed above. Anaemia and thrombocytopenia are the most common causes of clinical symptoms in pancytopenia, but leucopenia (while uncommon) can be life-threatening. Pancytopenia is often discovered by chance in a patient who is suffering from a condition that causes all cellular components in the blood to be depleted. A case of pancytopenia can have a wide range of clinical patterns, therapeutic options, and outcomes [2].

Pancytopenia has diverse aetiology- bone marrow depression due to any cause,or peripheral destruction as well as sequestration of formed elements of blood. Bicytopenia is a term used when only two parameters of a full blood count are low. The method of diagnosis is the same as for pancytopenia [3]. Pancytopenia can also occur due to the replacement of marrow by tumour or fibrosis. Management and prognosis of a patient of pancytopenia depends upon the underlying cause [4]. Mild marrow dysfunction is initially undetectable, and pancytopenia may manifest only at times of stress or high demand (bleeding, infection etc.,). The incidence of various disorders, causing pancytopenia, varies based on geographical distribution and genetic predispositions [5,6]. A study done at New Delhi found megaloblastic anaemia as the most common aetiology (28.4%) in children. Acute leukaemia and aplastic anaemia accounted for 21% and 20% cases, respectively [7]. Aplastic anaemia was shown to be the most common cause of pancytopenia in a study on pancytopenia among children in eastern India [8]. The identification of pancytopenia aetiologies in diverse regions can aid in the development of diagnostic and therapeutic techniques, which should lead to improved patient management. A disturbance of each of the principal blood elements is reflected much earlier and the changes are more conspicuous in the marrow than the peripheral blood [9]. Though Bone Marrow Aspiration (BMA) is most commonly done test, a dry or blood tap is also done, and even repeated attempts of BMA may fail to obtain sufficient marrow particles for adequate examination. Hence, a Bone Marrow Trephine Biopsy (BMTB) plays an important and ultimate role in this case [2]. BMTB along with imprint smear examination gives scope to the histopathological examination along with cytological details.

The aim of this study was to determine the aetiology of pancytopenia, as well as its prevalence and clinicopathologic characteristics within the study population.

MATERIALS AND METHODS

This hospital-based, cross-sectional, study was conducted in North Bengal Medical College and Hospital, Sushrutanagar, West Bengal, India, from July 2012 to June 2013. The study was conducted after getting clearance from the Institutional Ethical Committee.

Inclusion criteria: All children upto 12 years of age having pancytopenia (after examination of their complete haemogram), admitted in the Paediatric Department of the study hospital during the study period were included in the study. Pancytopenia was described as a haemoglobin concentration of <10 g%, a total white cell count of $<4\times10^9$/L, an Absolute Neutrophil Count (ANC) of <1,500/L, and a platelet concentration of <100,000/L.

Exclusion criteria: Patients already on definitive treatment for diseases causing pancytopenia, and those whose parents refused to take part in the study were excluded from the study.

Sample size calculation: From various previous studies it is seen that incidence of pancytopenia among children range from 2.9-3.1% [10,11]. Taking the maximum value of these findings, which is 3.1%, allowing for 5% margin of error (d) with 95% CI ($z_{\alpha/2}$=1.96) using single population proportion (p) formula, sample size calculated was

$n=(Z_{\alpha/2})^2\times p(1-p)/d^2=(1.96)^2\times0.031(0.969)/(0.05)^2=46$.

Procedure

A thorough history and clinical examination was done and the data was recorded in a self-designed proforma (identification of subject, present history, socio-economic status as per the BG Prasad classification, general survey findings, systemic examination findings) [12]. Specific characteristics of pancytopenia symptoms (fatigue, palpitation, shortness of breath, fever, and easy bruising) were also investigated.

Complete Blood Count (CBC) and Peripheral Blood Smears (PBS) tests were performed on blood samples. For PBS examination, the smear was stained with Leishman stain, and fresh methylene examination was used to identify the reticulocyte count. The CBC was calculated using the Sysmex KX21 automated cell counter and blood taken in the ethylenediaminetetraacetic acid vial. The Beckman Coulter Access 2 immunoassay system was used to check the levels of vitamin B12 and folate in the blood to diagnose the cases of megaloblastic anaemia. Salah's aspiration needle and Jamshidi trephine biopsy needle were used to aspirate and biopsy bone marrow under aseptic conditions. Simultaneous imprint preparation was done from the biopsy material. Leishman staining of the imprint smear was done for cytological details. Cytological and clinico-haematological diagnosis was done in all cases. Decalcification of the biopsy done for a fixed period. Haematoxylin and Eosin (H&E) staining of all the biopsy material was done. Reticulin staining (Gordon's and Sweet method) of the biopsy material, especially in case of hypoplastic/Aplastic anaemia was done. Periodic Acid Schiff's (PAS) staining of the biopsy was done in selected cases e.g., Acute Lymphoblastic Leukaemia (ALL).

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) Version 16.0 for windows (SPSS 16) was used. Arithmetic mean was calculated.

RESULTS

Total 6205 blood samples from Paediatric Department were examined, within one year of the study period. Out of that, 50 cases were diagnosed to have pancytopenia. The patients' peripheral blood films were examined for red, white, and platelet morphology, as well as the presence or absence of immature cells and blast cells. The morphology of all cell lineages, cellularity, parasites, and aberrant cells were all examined during the bone marrow examination. Mean age of the population was 7.3 years. There were total 24 males and 26 females [Table/Fig-1].

Age distribution	0-4 years (n, %)	5-8 years (n, %)	9-12 years (n, %)
Male	5 (55%)	9 (39%)	10 (55%)
Female	4 (45%)	14 (61%)	8 (45%)
Total	9	23	18

[Table/Fig-1]: Age and sex distribution.

Most commonly affected age group was 5-8 years. Most common cause of pancytopenia in this age group was megaloblastic anaemia [Table/Fig-2]. Aplastic anaemia was seen to be the most common cause of pancytopenia as a whole. Females were seen to be more commonly affected in aplastic anaemia and megaloblastic anaemia [Table/Fig-3]. Kala-azar, ALL, ITP were seen more in males. Generalised weakness was seen in all cases of pancytopenia followed by fever as most common presenting symptom. Pallor was most common presenting sign [Table/Fig-4]. [Table/Fig-5] shows the presenting symptoms and signs in individual causes of pancytopenia. Socio-economic status and residential details are mentioned in [Table/Fig-6,7].

Diseases	0-4 years (n=9)	5-8 years (n=23)	9-12 years (n=18)	Mean age (years)
Aplastic anaemia	5 (55%)	7 (30%)	10 (55%)	7.6
Megaloblastic anaemia	3 (33%)	8 (35%)	4 (22%)	6.9
Kala-azar	0	6 (26%)	3 (17%)	7.8
Acute lymphoblastic leukaemia	1 (11%)	2 (9%)	0	5.3
Idiopathic thrombocytopenic purpura	0	0	1 (6%)	9

[Table/Fig-2]: Causes of pancytopenia.

Diseases	Male (n=24)	Female (n=26)	Total (N=50)
Aplastic anaemia	9 (38%)	13 (50%)	22 (44%)
Megaloblastic anaemia	6 (25%)	9 (35%)	15 (30%)
Kala-azar	6 (25%)	3 (11%)	9 (18%)
Acute lymphoblastic leukaemia	2 (8%)	1 (4%)	3 (6%)
Idiopathic thrombocytopenic purpura	1 (4%)	0	1 (2%)
Total	24	26	50 (100%)

[Table/Fig-3]: Gender distribution based on aetiologies of pancytopenia.

Symptoms	Number of cases (%)	Signs	Number of cases (%)
Generalised weakness	50 (100%)	Pallor	50 (100%)
Fever	40 (80%)	Glossitis	15 (30%)
Anorexia	27 (54%)	Splenomegaly	11 (22%)
Petechial haemorrhage	16 (32%)	Pedal edema	10 (20%)
Cough	15 (30%)	Lymphadenopathy	6 (12%)
Vertigo	14 (28%)	Hyperpigmentation	6 (12%)
Breathlessness	13 (26%)	Hepatomegaly	3 (6%)
Abdominal fullness	11 (22%)	Sternal tenderness	2 (4%)
Arthralgia	5 (10%)		
Epistaxis	5 (10%)		
Malaena	3 (6%)		

[Table/Fig-4]: Presenting symptoms and signs.

DISCUSSION

Total 6205 blood samples from pediatric indoor were examined within one year of study period; out of which 50 cases were diagnosed to have pancytopenia, after examination of the complete haemogram. So, the incidence rate of pancytopenia among children was (50/6205×100)=0.80%. This is comparable to the studies of Dubey SRK et al., conducted at Kanpur UP and that by Chand R and Singh N., conducted at Kumaon region, noted

Diseases	Generalised weakness	Fever	Vertigo	Anorexia	Petechial haemorrhage	Pallor	Glossitis	Splenomegaly
Aplastic anaemia (n=22)	22 (100%)	19 (86%)	7 (32%)	15 (68%)	10 (45%)	22 (100)	5 (23%)	0
Megaloblastic anaemia (n=15)	15 (100%)	9 (60%)	6 (40%)	5 (33%)	3 (20%)	15 (100%)	8 (53%)	0
Kala-azar (n=9)	9 (100%)	9 (100%)	0	4 (44%)	0	9 (100%)	1 (11%)	9 (100%)
Acute lymphoblastic leukaemia (n=3)	3 (100%)	3 (100%)	1 (33%)	3 (100%)	2 (66%)	3 (100%)	0	2 (66.6%)
Idiopathic thrombocytopenic purpura (n=1)	1 (100)	0	0	0	1 (100%)	1 (100%)	1 (100%)	0

[Table/Fig-5]: Presenting symptoms and signs in individual cases of pancytopenia.
Splenomegaly was seen in Kala-azar and ALL

Diseases	I	II	III	IV	V
Aplastic anaemia (n=22)	1 (5%)	4 (18%)	2 (9%)	7 (32%)	8 (36%)
Megaloblastic anaemia (n=15)	0	1 (7%)	2 (13%)	5 (33%)	7 (47%)
Kala-azar (n=9)	0	1 (11%)	2 (22%)	2 (22%)	4 (45%)
Acute lymphoblastic leukaemia (n=3)	1 (33%)	0	0	1 (33%)	1 (33%)
Idiopathic thrombocytopenic purpura (n=1)	0	0	1 (100%)	0	0
Total	2	6	7	15	20

[Table/Fig-6]: Socio-economic status of pancytopenic patients against the specific diagnoses.
Majority of cases belonged to lower socio-economic status

Diseases	Rural (%)	Urban (%)
Aplastic anaemia (n=22)	16 (73%)	6 (27%)
Megaloblastic anaemia (n=15)	14 (93%)	1 (7%)
Kala-azar (n=9)	6 (67%)	3 (33%)
Acute lymphoblastic leukaemia (n=3)	2 (67%)	1 (33%)
Idiopathic thrombocytopenic purpura (n=1)	1 (100%)	0
Total	39	11

[Table/Fig-7]: Residential distributions of cases.
Majority of the cases were rural residents

the incidence of pancytopenia as 2.9%, and 3.04%, respectively [10,11]. Similarly, the study by Memon S et al., conducted at Pakistan, noted the incidence of pancytopenia as 3.57%, and that by Jha A et al., conducted at Nepal mentioned it as 15.74% [13,14]. This variance in pancytopenia incidence can be explained by the fact that pancytopenia is caused by a variety of disease processes that vary by population, age, nutritional condition, and exposure to the environment. In the present study, out of 50 cases, 26 (52%) were females and 24 (48%) were males with the male to female ratio 1:1.08. A study done by Osama I et al., at Rawalpindi, Pakistan, found the male to female ratio to be 1.1:1 [15]. Males had a higher incidence than females, according to Jalbani A et al., from Pakistan [16]. Some other studies from India also found higher incidence in males [17-20]. Only in very few study like that by Raphael V et al., in India higher incidence in female could be seen [21]. Male preponderance in prior research could be related to social/cultural taboos in society that make healthcare facilities more accessible to males than females, resulting in increased male presentation at hospitals, particularly in rural regions [10]. Mean age of pancytopenia in the present study was 7.3 years. Gupta V et al., found mean age to be 8.6 years [22]. In a study conducted in Kanpur by Dubey SRK et al., the average age of presentation was 10.63±4.60 years [10]. Out of 22 cases of aplastic anaemia, 10 were older than 8 years. In the index study, most common cause was found to be aplastic anaemia (44%) and megaloblastic anaemia (30%). Megaloblastic anaemia (47 percent), aplastic anaemia (25.8%), and leukaemia (17.6%) were the most common causes of pancytopenia, according to a study from Uttar Pradesh [10]. Another study from New Delhi reported that out of 109 children with pancytopenia, 31 (28.4%) had megaloblastic anaemia, followed by acute leukaemia (including ALL, AML, and myelodysplastic syndrome) and aplastic anaemia, which accounted for 21% and 20% of cases, respectively [7]. Study done in Pakistan found aplastic anaemia as the commonest cause followed by hypersplenism. Megaloblastic anaemia was the third most common cause [16].

The most prevalent presenting symptom in this study was generalised weakness (which accounted for 100% of the cases), followed by fever (80%). Pallor (100%) was the most prevalent presenting sign, followed by glossitis (30%). Pallor was also the common presenting sign (81%), in a study done at Uttar Pradesh, which was followed by fever (68%) and petechial haemorrhages (51%) [10].

Fever (51.8%) and pallor (59%) were the most common symptoms in children with pancytopenia, according to another study conducted in Chandigarh, Punjab. Petechial rash and bleeding were also typical symptoms. Hepatomegaly was detected in 51.8% of cases while splenomegaly was seen in 37.4% [23].

In this study, pancytopenia was found more in low socio-economic status. This may be correlated with the fact that megaloblastic anaemia is associated with malnutrition which is more common in low socio-economic status. It is also seen in other studies that aplastic anaemia is linked with lower socio-economic status [24,25]. Lower socio-economic status, which is widespread in this population, is an indirect sign of higher exposure to environmental variables linked to aplastic anaemia pathogenesis [24]. Low socio-economic status could be a proxy for one or more environmental conditions that can lead to aplastic anaemia, such as pathogenic infections or chemical exposures [25]. In this study, pancytopenia was common among rural population than urban. Similarly, other studies also reported a rural predominance of aplastic anaemia [10,26]. But no proper explanation has been found for this finding. In this study predominance of patients from rural area may be a reflection of distribution of local population attending the hospital.

Pancytopenia is a haematological disorder that affects a large number of people. There is, however, a scarcity of information about the underlying causes of pancytopenia. Variations in the frequency of various aetiologies causing pancytopenia have been attributed to a variety of factors, including differences in diagnostic criteria, study period, laboratory investigations used, geographic area, genetic differences in the study population, and varying exposure to cytotoxic agents [17].

As a result, comparable studies including large sample sizes from different parts of the country should be promoted. This will go a long way toward establishing adequate clinical faculties for managing important diseases including aplastic anaemia and haematological malignancies. Such research will not only aid in a better understanding of the underlying illness processes that contribute to pancytopenia, but it will also aid in the better management for patients with pancytopenia.

Limitation(s)

However, because this is a cross-sectional observational study conducted in a referral tertiary care hospital, there is a risk of selection bias, and the exact causes of pancytopenia prevalent in the region may not have been reflected. As a result, the authors recommend that larger studies be conducted to determine the most common cause of pancytopenia in this area.

CONCLUSION(S)

Pancytopenia is a common haematological disease in clinical practices, and it should be considered when a patient appears with unexplained anaemia, weight loss, splenomegaly, and a persistent fever. BMA is a useful diagnostic technique for determining the cause and severity of pancytopenia. Aplastic anaemia was the most common cause of pancytopenia in this study (44%), followed by megaloblastic anaemia (30%). Kala-azar (18%) was the primary cause of non haematological reasons. The current study shows that primary haematological examinations, as well as bone marrow examination, are beneficial in understanding the illness process and diagnosing the causes of pancytopenia in pancytopenia patients. This study also shows that kala-azar and megaloblastic anaemia should be considered in the differential diagnosis of pancytopenia. Clinicians, particularly primary care physicians and pathologists, should be aware of the many aetiology and morphological aspects of pancytopenia that can be found in this part of India. This knowledge can help to avoid not just delays in diagnosis, but also unneeded laboratory tests that could impair the patient's health and wallet.

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