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RESEARCH ARTICLE

A STUDY ON CYTOPENIAS AND THE FACTORS ASSOCIATED WITH CYTOPENIAS AMONG HIV INFECTED PATIENTS ADMITTED AT A TERTIARY CARE HOSPITAL.

Dr. Manju Rose Sebastian, Dr. Seenar Sankar and Dr. Mary George

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Abstract

Introduction: India has the third highest burden of HIV in the world. Haematological complications are common in HIV patients, of which cytopenias are the most frequently encountered. The cytopenias have been found to adversely affect the outcome of HIV patients with greater mortality and decreased quality of life. Aims and Objective: To assess the prevalence of cytopenias among patients admitted in a tertiary care hospital and to assess the factors associated with the cytopenias. Materials and Methods: The present study was conducted in the department of general medicine at a tertiary care hospital and 191 patients admitted in the hospital during the study period were taken for the study. The baseline investigations at the time of admission were taken into consideration. Patients were interviewed and charts reviewed to collect the data. The data collected was analysed with SPSS-2018. Continuous variables were expressed as mean \pm standard deviation and as median and interquartile ranges as appropriate. Categorical variables were expressed as percentages and frequencies. Comparisons between data was done by student's t test and chi square. The factors associated with various cytopenias was assessed using log binomial regression. A p value of < 0.05 was taken as significant. Results: The overall prevalence of any cytopenia was found to be 85.9%. The most common cytopenia was anaemia with a prevalence of 78.5% followed by thrombocytopenia and leucopenia with prevalences of 28.8% and 24.1% respectively. Anaemia was found to be more prevalent among females with a prevalence ratio of 3.05 (95% CI: 1.39- 10.16, p value 0.009) when compared to males. The most common cause of anaemia was found to be B12 deficiency. There was significant association between leucopenia and CDC staging with the prevalence of leucopenia being higher among patient with CDC stage 3. [Prevalence ratio:1.46 (95% CI 0.67-3.17, p 0.024)]. No significant association was found with gender, duration of HIV, ART regimen, CDC stage or presence of opportunistic infections and thrombocytopenia. Conclusion: The prevalence of cytopenias among HIV patients was found to high – 85.9% especially compared to other developed countries. The most common cytopenia among the patients was found to be anaemia with a prevalence of 78%. The next most common cytopenia was thrombocytopenia, followed by leucopenia. The factors associated with these cytopenias can help to screen for patients at higher risk of

developing these cytopenias and hence establish preventive strategies against them.

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Introduction:-

The national adult prevalence of HIV in India is 0.22% as per the India HIV estimation report 2017. The national prevalence is higher among males (0.25%) as compared to females (0.19%). Although there has been a consistent decline in the national prevalence in the recent years, Karnataka is one of the few states with a higher than national prevalence levels (0.47 %)¹. Since India has the third highest burden of HIV in the world based on absolute numbers, any study regarding this national pandemic is of utmost importance in formulating treatment and prevention strategies.

Among the various haematological abnormalities associated with HIV, cytopenias are the most common. Of these, anaemia is the most commonly encountered cytopenia. The presence of these cytopenias are often associated with faster disease progression, poor survival and prognosis^{2,3}. Anaemia was found to be an independent risk factor for morbidity. Neutropenia is associated with an increased risk of fungal infections and thrombocytopenia predisposes to bleeding manifestations⁴.

HIV results in cytopenias through various mechanisms – primarily through the effect of the virus on the survival and growth of the hematopoietic progenitors. Secondary causes of the cytopenia include the effect of various drugs, opportunistic infections and other co-existing infections⁴. There have been numerous studies regarding haematological profile and cytopenias in HIV patients. However, majority of these studies were centered in developing countries in Africa. Since the patient profile is significantly different, there is need for more Indian based studies regarding the same.

This study aims to estimate the prevalence of various cytopenias among the HIV patients admitted in a tertiary care hospital and to assess the various factors associated with such cytopenias.

Objectives

Primary Objective- To study the prevalence of various cytopenias among in-patient PLHIV

Secondary Objective- To assess the various factors associated with cytopenias among PLHIV

Materials and Methods:-

Sources of Data

Patients diagnosed with HIV admitted as inpatients in the department of general medicine, St Johns medical college Hospital, Bangalore were taken up for the study considering the inclusion and exclusion criteria.

Study design

Cross sectional descriptive hospital-based study

Duration of Study

1 year (November 2017 – November 2018)

Sample size

Based on a previous similar study conducted where the prevalence of observed cytopenia was 67%, using a 12% precision and 99% confidence level, the sample size was calculated to be 191.⁵

Inclusion criteria

All patients diagnosed to have HIV admitted in the inpatient department of St Johns Medical College Hospital.

Exclusion criteria

All patients with known haemoglobinopathies and malignancies, chronic kidney disease and chronic liver disease patients.

Method of Data Collection

After admission a detailed history was obtained from the patients and patients with known hemoglobinopathies, malignancy, chronic kidney disease and chronic liver disease were excluded from the study. Among those who were admitted, data regarding the cytopenias were obtained from the inpatient charts and data regarding the CD4 count and CDC stage was obtained from the ART centre book provided to the patient and the data so collected were analysed. Cytopenia was defined as presence of either anemia, leucopenia or thrombocytopenia. Anaemia was defined as haemoglobin less than 12g% in females and less than 13g% in males⁶. Thrombocytopenia and Leucopenia were defined as platelet count of less than 1.5Lakhs/cu.mm and total count less than 4000cells/cu.mm respectively. Only the baseline investigations at the time of admission to the hospital were considered. Patients were interviewed, evaluated and charts reviewed to obtain the data.

Statistical Analysis

The data collected was analysed using the SPSS – 2018 software and was represented using charts and tables. Univariate analysis was used to describe the subjects' characteristics. Continuous variables were expressed as mean +/- standard deviation and as medians and interquartile ranges as appropriate and categorical variables were expressed as percentages and frequencies. Comparisons between data was done by student's t test, Mann Whitney U test and chi square. Binomial regression was used to investigate the factors associated with each of the cytopenias. Odds ratio and the confidence intervals were described for this. A p value of < 0.05 was considered significant.

Results:-

A total of 191 patients were included in this study of which there were 131 males (68.7%) and 60 (31.3%) females. The mean age among males and females was 43.4±10.2 years and 42.8±11.3 years respectively. 37.7% of the patients were newly diagnosed with HIV. It was found that 42.7% of the patients were not on any ART at the time of the study this includes the patients who hadn't been initiated on HAART and those who had defaulted treatment. Among the 57.3% of patients on ART, it was seen that majority (63.7%) were on the non zidovudine based HAART regimen (Tenofovir/lamivudine/efavirenz regimen). Among the 191 patients, 54 (28.27%) didn't have any recent CD4 count – these included the newly diagnosed patients who hadn't been registered in the ART centres yet. In the rest of the patients in whom a recent CD4 count was available, it was found that majority (54.7%) were in the CDC stage III with AIDS defining opportunistic infections. The most common opportunistic infection noted was tuberculosis (70.5%). Interestingly 85.9% of the patients had one or more forms of cytopenia. Anaemia was the most common form of cytopenia (78.5%), followed by thrombocytopenia (28.8%) and leucopenia (24.1%). 42.9% of the patients had bicytopenia, and 6.3% had pancytopenia. The mean haemoglobin in this study was 10.2±2.9g%. The median leucocyte count was 5.8 x 10³/uL (IQR 4.0 - 8.3 x10³) and the median platelet count was 1.96Lakhs/uL (IQR 1.31-2.58Lakhs/uL). [Table 1- II]

Table 1:- Characteristics and haematological values of the study population (N= 191)

Characteristics	Statistics
Age (Years)	43.2 ±10.5
Sex- Females	60(31.3%)
Newly diagnosed HIV	72 (37.7%)
Patients not on ART	81 (42.7%)
Patients with opportunistic infections	61 (31.9%)
Tuberculosis (Any)	43 (70.5%)
Pneumocystis pneumonia	8 (13.1%)
CD4 count	185 (IQR 55- 372)
Hemoglobin (g%)	10.2±2.9
Total leucocyte count (x10 ³ /uL)	5.8(IQR 4.0-8.3)
Platelet count (Lakhs/UL)	1.96Lakhs/uL (IQR 1.31- 2.58)

Anaemia was found to be associated with female gender. The prevalence ratio of anaemia among females was found to be 3.05 as compared to males (95% CI 1.39- 10.16, p value 0.009). Although the prevalence of anaemia was found to be higher among CDC stage III disease, patients with newly diagnosed HIV and those with opportunistic infections, this difference was not statistically significant. [Table III]

The prevalence of leucopenia was higher among females than males, among patients not on any ART, those with opportunistic infections and newly diagnosed with HIV; however, none of these showed statistical significance. The prevalence of leucopenia was higher among CDC stage III patients with a prevalence ratio of 1.46 (95% CI 0.67-3.17, p value 0.024) as compared to other CDC stages on univariate analysis. On multivariate analysis, this difference was not statistically significant. [Table IV]

Thrombocytopenia had higher prevalence among males, patients on 2nd line ART regimen, unknown CDC stage and those with opportunistic infections but with no statistical significance.[Table V]

Table II :-Distribution of cytopenias among study population

Characteristics	N	% Anemia	% Leucopenia	% Thrombocytopenia
All participants	191	78.5	24.1	28.8
Gender				
Male	131	73.2	31	32.8
Females	60	90	25	20
CDC stage				
Unknown*	54	79.6	25.9	37.1
Stage I	25	68	8	16
Stage II	37	75.6	13.5	27
Stage III	75	62.9	33.5	28
ART Regimen				
Not on ART	81	81.5	28.4	30.9
1 st line AZT	15	73.3	26.7	20
1 st line non ZT	70	82.9	18.6	27.1
2 nd line	23	65.2	26.1	34.7
3 rd line	2	0	0	0
Opportunistic infections				
None	130	78.1	22.3	27.5
Presence of infection	61	83.6	27.8	31.7
Duration of HIV				
Newly diagnosed				
< 5years	72	79.1	26.4	28.2
>5years	64	13.7	20.9	29.8
	55	27.3	23.2	27.1

Table III :- Factors associated with anemia

Covariate	Univariable PR (95% CI)	p value	Multivariable OR (95% CI)	p value
Gender				
Male	1	0.009	1	0.009
Female	3.05 (1.21 -7.71)		3.76 (1.39-10.16)	
CDC stage				
Unknown stage	1			
Stage I				
Stage II	0.54 (0.18-1.58)	0.26		
Stage III	0.79 (0.29-2.17)	0.66		
	1.20(0.49-2.93)	0.68		
ART Regimen				
Not on ART	1			
1 st line AZT	0.99 (0.21-4.63)	0.99		

1 st line nonAZT	1.29 (0.46-3.56)	0.63		
2 ND line	0.42 (0.13-1.33)	0.33		
3 rd line	0	0.99		
Opportunistic infections				
Absent	1	0.63		
Present	1.25 (0.50-3.16)			

Table IV:-Factors associated with leucopenia

Covariate	Univariable PR (95% CI)	p value	Multivariable OR (95% CI)	p value
Gender				
Male	1	0.84		
Female	1.075 (0.53-2.19)			
CDC stage				
Unknown stage	1			
Stage I	0.25 (0.05-1.12)	0.08		
Stage II	0.45(0.15-1.37)	0.16		
Stage III	1.46(0.67-3.17)	0.024	1.43(0.61-3.37)	0.41
ART Regimen				
Not on ART	1			
1 st line AZT	0.92 (0.26-3.13)	0.89		
1 st line non AZT	0.58 (0.27-1.24)	0.16		
2 ND line	0.89(0.31-2.54)	0.83		
3 rd line	0			
Opportunistic infections				
Absence	1			
Presence	1.39 (0.69-2.79)	0.35		

Table V:- Factors associated with thrombocytopenia

Covariate	Univariable PR (95% CI)	p value	Multivariable OR (95% CI)	p value
Gender				
Male	1			
Female	0.51 (0.25-1.07)	0.07		
CDC stage				
Unknown stage	1			
Stage I	0.32(0.09-1.08)	0.06		
Stage II	0.63(0.25-1.56)	0.32		
Stage III	0.67(0.32-1.42)	0.30		
ART Regimen				
Not on ART	1			
1 st line AZT	0.56(0.14-2.16)	0.40		
1 st line non AZT	0.83(0.41-1.69)			
2 ND line	1.12 (0.49-3.18)	0.62		
3 rd line	0	0.72		
Opportunistic infections				
Absence	1			
Presence	1.22(0.63-2.38)	0.55		

Discussion:-

The total number of patients included in this study was 191. The majority of patients in this study were males in accordance to the national gender wise prevalence in which males had a higher prevalence of 0.25% as compared to

females 0.19%¹. The mean age of the patients in this study was 43.2 ± 10.7 years with majority of the patients being middle aged (age group 36-55 years). Nationwide statistics have shown a decline in the prevalence of HIV/AIDS among young adults hence explaining the higher prevalence among the middle aged groups. This is probably in connection with the improved preventive programmes against the disease.

Majority of the patients in this study were those newly diagnosed as HIV positive and hence were not on any form of ART at the time of the study. This represents the newly diagnosed patients who would be initiated on ART after ruling out opportunistic infections and by registering in ART centres close to their residences. Among the patients on ART, majority were on the non zidovudine based first line regimen – namely the tenofovir/lamivudine/efavirenz regimen. This is in accordance to the ART guidelines where this is the regimen of choice⁷. Around 28% of the patients didn't have a CD4 count at the time of the study. CD4 testing is done as part of registration and initiation of therapy in ART centres. No extra investigations were conducted as part of this study and hence the newly diagnosed patients didn't have CD4 counts done. These patients were taken to be the CDC Unknown stage during the classification. The most common opportunistic infection was Tuberculosis (both pulmonary and extrapulmonary). Recent studies have also shown that Tuberculosis is the most common opportunistic infection among HIV patients in India^{8,9}.

The overall prevalence of cytopenias was found to be 85.9%. The most common cytopenia was anemia which is in concordance to other similar studies. The prevalence of anaemia was 78.5% which is comparable to the high prevalence noted in similar studies conducted in India as well as other developing countries in Africa. The study done in Chandigarh found the prevalence of anaemia to be 65.5%¹⁰. The higher prevalence in our study could be attributed to the fact that this study was conducted in a tertiary multispecialty centre catering to a wider population base as compared to the study in Chandigarh. The study conducted in Varanasi, catering to a similar wide population base showed comparable results with prevalence of anaemia of 74.6%¹¹. In the study done by Kyeyune et.al in Uganda among patients initiating HAART, the prevalence of anemia was found to be less than this – 47.8%¹². The difference could be probably due to the geographical and population factors. This is similar to the findings by Fekene et al where the prevalence of anaemia among HIV patients in Ethiopia was found to be 51.5%¹³. The higher prevalence seen in India as compared to other developing countries stresses the importance of early diagnosis and management of anaemia.

The next most common cytopenia noted in the study was thrombocytopenia with a prevalence of 28.8%. The prevalence of thrombocytopenia among similar studies conducted in India was found to range between 7%-41%^{10,11,14}. Whereas the prevalence of thrombocytopenia in studies done outside India (African continent) was found to be much less ranging between 5- 15%^{12,13,15}. The great variation noted in the prevalence of thrombocytopenia could be owing to the difference in the laboratory cut offs used for definition of thrombocytopenia as well as the other factors that can cause a confounding thrombocytopenia such as giant platelets and presence of platelet aggregates.

In this study the prevalence of leucopenia was found to be 24.1% which was comparable to other studies in India as well as other studies outside India that showed a prevalence range 20-30%^{10,11}. Anemia was found to be associated with gender with a higher prevalence in females compared to males. This is in concordance with a similar study conducted in Uganda¹² and can be attributed to the fact that women are more prone to anaemia in view of blood loss during menstrual cycles, pregnancy and childbirth. The study in Varanasi as well as the study in Sao paulo showed an association of anaemia with CD4 count which was not established in this study^{11,16}. The prevalence of anaemia was found to be higher in CDC stage 3 as compared to stage 1 but the difference was not statistically significant. A limitation in the present study was the number of people in the CDC stage unknown which could have probably influenced the results.

Although the ART medication Zidovudine is known for its side effect of macrocytic anaemia, in this study it was found that there was a higher prevalence of anaemia in the non zidovudine based regimen. This can probably be explained by the fact that patients on the Zidovudine regimen undergo close scrutiny to detect anaemia and are subject to regimen change at the earliest detection of anaemia unlike the other regimens.

Of the 150 patients who had anaemia, the most common cause of anaemia was found to be B12 deficiency (47.3%), followed by anaemia of chronic disease (32.7%). Iron deficiency anaemia was seen in 9.3% of patients with anaemia. Previous studies have shown that HIV infection predisposes to B12 deficiency due to the malabsorption

and due to the changes that occur in the B12 binding and transport proteins. B12 deficiency has been found to be associated with an adverse outcome in HIV patients¹⁷. DCT was positive in 3 of the patients but AIHA confirmed in only one of these patients. DCT positivity has been reported previously in advanced HIV disease with no other obvious evidence of haemolysis and was suggested as a prognostic factor in the clinical course of the disease¹⁸

The most common pattern of anaemia was seen to be normocytic normochromic type (51%) followed by normocytic hypochromic (21.3%). Although B12 deficiency was the most common cause of anaemia, the macrocytic pattern on peripheral smear was found in only 4.6%. A similar study done in Ethiopia showed that normocytic normochromic pattern was the most common pattern followed by macrocytic pattern¹³. The higher prevalence of macrocytic pattern in the study done in Ethiopia could be due to the fact that many of the patients were on the zidovudine based regimen unlike the present study.

Leucopenia was found to be associated with the CDC stage but not with gender, ART regimen, duration of HIV or opportunistic infections. The higher prevalence of leucopenia was in patients of CDC stage 3. This is comparable with the other studies done in Uganda, Ethiopia and Sao Paulo that show a greater prevalence of leucopenia with greater immunosuppression – lower CD4/ CDC stage 3.^{12,13,16} A study done in Tanzania demonstrated an association of leucopenia with female gender¹⁵. This association was not confirmed in the present study or similar other studies. Thrombocytopenia was not found to have association with gender, CDC stage, ART regimen, duration of HIV or opportunistic infection. Previous studies in Tanzania and Sao Paulo have shown an association between CD4 count and level of immunosuppression with thrombocytopenia^{12,16}. This study did show a high prevalence of thrombocytopenia among CDC stage III but the difference was not statistically significant. A high prevalence of thrombocytopenia was also seen among patients of unknown CDC stage. A similar study in Mysore and in Chandigarh demonstrated no association between thrombocytopenia and CD4 count^{10,14}. In this study the large number of patients with an unknown CD4 count probably influenced the results and hence a reasonable conclusion on the association of cytopenias and level of immunosuppression couldn't be made. The study in Ethiopia showed a higher prevalence of thrombocytopenia among patients on the non AZT regimen as compared to patients on the AZT based regimen¹³. The explanation given for this was that zidovudine can rapidly increase platelet count in HIV related thrombocytopenia. This finding however, has not been corroborated in this study as well as other similar studies and requires further research.

In conclusion, as cytopenias are the most common haematological abnormalities seen in HIV patients, the importance of constant monitoring of blood counts and early identification of such cytopenias cannot be stressed enough. As they directly impact the life of HIV patients, it becomes imperative for the early diagnosis and management. However, as this study had limitations in the small sample size, deficiencies in data such as CD4 counts and the confounding factors such as acute febrile illness which influence the blood counts, it is necessary for more such studies to evaluate the factors associated with cytopenias allowing for better screening of patients at higher risk of developing them.

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Conflicts Of Interests

Nil.

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