Original Research Article

Study of haematological abnormalities in HIV infected patients and its correlation with CD4 counts

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ABSTRACT

Background: To study and correlate the haematological abnormalities with CD4 cell counts in HIV infected patients diagnosed on OPD basis in S.C.B Medical College, Cuttack, before they are initiated on Antiretroviral (ARV) therapy.
Methods: A 100, ELISA positive, untreated HIV patients were included in the study while those patients with history of any haematological disease, Chronic Kidney Disease (CKD), Chronic Liver Disease (CLD), underlying malignancy or on chemotherapy were excluded. Following clinical evaluation, haemoglobin levels (Hb. %), Total Leucocyte Count (TLC), Differential Leucocyte Count (DLC), Erythrocyte Sedimentation Rate (ESR), Platelet Count (PC), CD4 counts (by flow cytometry) and peripheral smear examination was done. They were staged as per WHO clinical staging guidelines given by NACO and statistical analysis was drawn by Fischer Exact Test and association between CD4 counts and haematological abnormalities were inferred.
Results: The mean age of the patients was found to be 36.85±6.2 years with males (63%), married (80%) and rural population (78%) showing commonest mode of transmission of the virus as heterosexual route (94%). Most common clinical finding was found to be pallor (68%) with majority in stage III of AIDS. Mean TLC count was found to be 5872±2210 cells/mm 2.40% had leucopenia on TLC and 29% had neutropenia, 30% lymphocytopenia and 20% monocytopenia on DLC. Mean CD4 count was 89 cells per microliter and 79% were anaemic. CD4 counts did not statistically correlate either with WHO staging or cytopenias or haemoglobin levels. However, there was positive association between CD4 counts with anaemia, WHO stages of AIDS, lymphocytopenia and monocytopenia in this study.
Conclusions: In this study we could ascertain that, majority were in WHO stage III of AIDS with CD4 counts <200 cells per microliter and blood findings of various cytopenias and anaemia. From our findings, we could correlate between WHO stage of AIDS, CD4 counts and haematological abnormalities thus, establishing the essence of our study.

Keywords: AIDS, CD4 counts, Cytopenias, Clinical, Correlation, Haematological, HIV

INTRODUCTION

Since the first case of AIDS in the world reported in the U.S.A in 1981, Human Immunodeficiency Virus (HIV) infection or Acquired Immunodeficiency Syndrome

(AIDS) became a global pandemic affecting more than 33 million people by the year 2009 and emerged as a major challenge for health care across the world.[1] It was named AIDS by Centre for Disease Control (CDC), U.S.A. in 1982.[2] India reported its first case of AIDS in 1986 and since then it has affected majority of Indian population being most prevalent in Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur and Nagaland.[3,4] States of Odisha, Bihar, West Bengal, Uttar Pradesh, Rajasthan, Madhya Pradesh, Gujarat together account for 41% of new cases of AIDS.[5] In Odisha, Ganjam district has the highest (38%) incidence in southern Odisha while Cuttack has the highest (3.2%) incidence in coastal Odisha.[5] HIV is an enveloped retrovirus that primarily affects the body's immune system by targeting the T-lymphocytes and replicates itself by using DNA of CD4+ T cells thus, depleting their numbers and making the individual prone to opportunistic infections within a matter of months to years eventually leading to the death of the patient. HIV has two variants, HIV-1 and HIV-2 with HIV-1 being the major cause of AIDS worldwide. HIV-1 has A,B,C,D,F,H,J and K subtypes among which subtype C is predominant in India and while HIV-2 has only 2 reported subtypes i.e. A and B (found mostly in West Africa) none of which are prevalent in India.[6] Sexual transmission among heterosexuals accounts for the most prevalent mode of transmission of HIV-1 followed by parent to child (vertical) transmission, i.v. drug users, homosexuals and blood transfusion respectively.[7] HIV on entering the host spreads extensively to cells and tissues progressively destroying lymphnode architecture thus prompting the host's immune system to mount a response against it through CD4+ T cells and CD8+ T cells which in turn get destroyed by the virus allowing free HIV replication ultimately leading to full-fledged AIDS.[8] Following primary infection, AIDS remains as an acute infection for weeks. During mid-stages of the disease which lasts for months to years, there is presence of lower range of HIV RNA and viral antigen in the peripheral blood which is called 'set point' and it predominantly manifests as generalized lymphadenopathy in some patients. In advanced stages i.e. with CD4 count <200 cells per microliter opportunistic infections commonly occur thus qualifying as CDC- defined AIDS.WHO clinical staging classifies AIDS into 4 stages based on symptoms and clinical signs and opportunistic infections starting from an asymptomatic Stage I progressing to HIV wasting syndrome seen in Stage IV. Haematological abnormalities secondary to HIV infection include anaemia, neutropenia, thrombocytopenia, venous thromboembolism, AIDS related lymphoma, Castlemann's disease and rarely Hodgkin's disease and myeloma with anaemia being detected in 10% to 20% at initial presentation of cases and 70% to 80% of cases as the disease progresses.[9,10] Anaemia in AIDS primarily depends on CD4 count and increased viral load leading to decreased production of RBCs or increased destruction of RBCs or ineffective production of RBCs.[11] Moove and colleagues found that the risk of bacterial infections increases to 2.3 fold and 7.9 fold in HIV infected cases with absolute neutrophil count less than 1000/ml and 500/ml respectively.[12] Similarly, lymphopenia (CD4+ T cell count <200 cells per microliter) there is high risk of opportunistic infections like pneumocystis carnii, cytomegalovirus, mycobacterium avium and candidial thrush. Thrombocytopenia is common (40%) in HIV cases accounting for 10% of first symptom or sign.[13,14] With thrombocytopenia there is high risk of developing HIV related Idiopathic Thrombocytopenic Purpura (ITP) and Thrombotic Thrombocytopenic Purpura (TTP). Aim of our present study was focussed on establishing the correlation between CD4 counts in HIV infected individuals and their haematological abnormalities considering the increased number of new HIV cases in this state attending OPDs which will provide clear data for future reference when initiating ARV therapy.

METHODS

One hundred HIV infected cases (confirmed by positive ELISA test), not initiated on ARV therapy having mean age of 36.85±6.2 years were included in the study. Patients with established haematological diseases, CKD, CLD, malignancies or with any history of receiving chemotherapy were excluded. Out of these 100, 63% were males, 80% were married and 78% were found to be of rural areas. After thorough history taking and detailed general and systemic examination, laboratory work up like haemoglobin levels, TLC, DLC, ESR, LFT, serum creatinine, serum sodium, serum potassium, lipid profile, urine routine microscopy, CD4 counts by flow cytometry and examination of peripheral blood smear was done. Subsequently, all data were collected, compiled and compared and values were presented as mean±standard deviation and median ±Q (interquartile range) and appropriate statistical association was drawn by using Fischer Exact Test, between CD4 counts and haematological abnormalities. Percentages were used to describe proportions of discrete variables and a p value of less than 0.05 was considered statistical significant.

RESULTS

Our study group of 100 HIV infected patients consisting of males 63% and females 36% (with 80 % married) were found to be in different age groups of 21-25, 26-30, 31-35, 36-40, 41-45, 45-50 and 51-85 years as 2%, 15%, 29%, 27%, 20%, 5% and 2% respectively with mean age of 36.85 ±6.2 years. The mode of transmission of HIV in this study was found mostly to be heterosexual (94%) followed by i.v drug abuse (4%) and vertical transmission (2%). On general examination, pallor was found to be most common (68%) clinical sign with other signs being lymphadenopathy (10%), pedal oedema (6%), cyanosis (4%) and skin rash (4%). Majority of them were in stage III (55%) and least were in Stage I (4%) as shown in Table 1. The mean total count was found to be 5872±2210 cells/mm^2 with 40 of them being leucopenic as presented in Table 2 and DLC results showed

neutropenia in 29, lymphocytopenia in 30 and monocytopenia in 20 of the patients with their mean values being depicted in Table 3.

Table 1: WHO stage distribution.

Stage	N	%
I	4	4
II	29	29
III	55	55
IV	12	12

Table 2: Total count distribution.

Total count (Cells/mm^3)	N	%
2000-3000	9	9
3001-4000	22	22
4001-5000	11	11
5001-6000	13	13
6001-7000	8	8
7001-8000	14	14
8001-9000	16`	16
9001-10000	7	7

Table 3: Differential count.

White Blood Cells	Mean
Neutrophils	54±12.6%
Lymphocytes	29.8±8.3%
Monocytes	6.76±4.1%
Eosinophils	2.36±3.79%
Basophils	0%

As inferred from the data in Table 4, the mean CD4 count was 89 cells/microlitre with 87 % of the patients enrolled in this study having CD4 count <200 cells/microlitre out of which 30% were having lymphocytopenia thus establishing a positive association (P<0.05) between lymphocytopenia and low CD4 counts as shown in Table 5.

Table 4: CD-4 count distribution.

CD4 Count (Cells / microlitre)	n	%
<200	87	87
200-499	13	13
≥500	0	0

Table 5: Correlation between lymphocyte and CD4 count.

Lymphocyte (%)	CD4 < 200	CD4 ≥200	Total	Fisher exact test
<22%	30	0	30	P=0.0310
≥22%	59	11	70	

Results showed 25% patients having haemoglobin levels in the range of 11-11.99 and 23% in 10-10.99, with the

mean haemoglobin value being 11.40±1.36g/dl and thus, anaemia was found in 79% cases with 55% being males and 24% females as presented in Table 6. Normocytic Normocromic Anaemia (NNA) was seen in 56% of cases of anaemia followed by Microcytic Hypochromic Anaemia (MHA) and Dimorphic Anaemia (DMA) in 15% and 8% of cases respectively and 21% showing Normocytic Normocromic Blood Picture (NNBP) as shown in Table 7.

Table 6: Haemoglobin distribution.

Haemoglobin g/dl	Male	Female	%
8.0-8.9	1	1	2.0
9.0-9.99	10	3	13.0
10.0-10.99	12	11	23.0
11.0-11.99	16	9	25.0
12.0-12.99	16	13	19.0
13.0-13.99	8	0	08.0

Table 7: Types of anaemia.

Blood picture	Number of patients	%
NNBP	21	21
NNA	56	56
MHA	15	15
Dimorphic Anaemia	8	8
Total	100	100

The WHO clinical stage wise analysis of the haematologic abnormalities were not found to be statistically significant as presented in Table 8. Hence, no possible association between WHO Stages and cytopenias could be drawn. However, the WHO clinical stages and anaemia correlation was found to be statistically significant depicted in Table 9.

Table 8: WHO Stage wise distribution of haematological abnormalities.

Abnormalities	I	II	III	IV	P
Leucopenia	2	11	21	6	0.87
Neutropenia	2	9	16	2	0.62
Lymphocytopenia	-	9	18	3	0.56
Monocytopenia	-	5	11	4	0.49
Thrombocytopenia	2	12	21	6	0.57

Table 9: WHO staging and anemia.

Anemia	I	II	III	IV	P
Male	-	12	35	8	0.04
Female	0	10	13	1	0.005

In the study results correlation between CD4 count and haemoglobin levels in both males and females was found insignificant (p>0.05) as in patients having CD4 count <200 cells per microlitre, 70% had anaemia and those

having CD4 count >200 cells per microlitre only 9% had anaemia as presented in Table 10 and 11.

Table 10: Correlation between Hb and CD4 count in male.

Hb(g/dl)	CD4 <200	CD4 ≥200	Total	Fisher exact test
<13	48	7	55	P= 1.00
>13	7	1	8	

Table 11: Correlation between HB and CD4 count in female.

Hb (g/dl)	CD4 <200	CD4≥200	Total	Fisher exact test
<12	22	2	24	P=1.000
≥12	10	3	13	

Correlation between TLC and CD4 count was found not to be significant (p>0.05) as 36% patients with CD4 counts <200 cells per microlitre and 4% patients with CD4 counts >200 cells per microlitre had leucopenia as presented in Table 12. 26% of patients with CD4 count <200cells/microlitre and 3% with CD4 count ≥200cells/microlitre had neutropenia and thus, correlation found to be not significant (p>0.05). Similarly, with 26% of patients with CD4 count <200cells/microlitre and 3% with CD4 count ≥200cells/microlitre having neutropenia correlation between neutropenia and CD4 count was found to be not significant (p>0.05) as shown in Table 13.

Table 12: Correlation between total count and CD4 count.

Total Count (cells/mm³)	CD4 <200	CD4 ≥200	Total	Fisher exact test
<4500	36	4	40	P=0.5547
≥4,500	51	9	60	

Table 13: Correlation between neutrophil and CD4 count.

Neutrophil (%)	CD4 <200	CD4 ≥200	Total	Fisher exact test
<40%	26	3	29	P= 0.7512
≥40%	61	10	71	

The results showed that 17% with CD4 count <200cells/microlitre and 3% with CD4 count ≥200cells/microlitre had monocytopenia and hence, the correlation was found not to be significant (p>0.05) as reflected in Table 14.

Results also show 35% of patients with CD4 count <200cells/microlitre and 6% with CD4 count ≥200cells/microlitre had thrombocytopenia. Therefore,

correlation between platelets and CD4 count found to be not significant (p>0.05) as depicted in Table 15.

Table 14: Correlation between monocyte and CD4 count.

Monocyte (%)	CD4 <200	CD4 ≥200	Total	Fisher exact test
<4%	17	3	20	P=0.7200
≥4%	70	10	80	

Table 15: Correlation between platelets and CD4 count.

Platelets (lakh/mm³)	CD4 <200	CD4 ≥200	Total	P value
<1.5	35	6	41	P=0.7663
≥1.5	52	7	59	

DISCUSSION

Being a tertiary hospital our selection of cases was more precise, hence a square number of 100 cases were chosen for statistical convenience. These HIV positive patients (not initiated with any antiretroviral therapy) were analysed with respect to their haemoglobin levels, TLC, DLC, platelet count, ESR and peripheral blood picture and CD4 counts and inference was drawn. The mean age of the population was 36.85±6.29 years, 56% of which were in 31 to 40 years age group which is in concordance with Odisha state AIDS control society and NACO annual report 2009-10.[8,15] Male to female ratio was found to be 3:2 which establish that more males are affected with HIV. Moreover, in this study we found that 80% out of 100 patients were married which is consistent with the study by Ghiya, et al.[16] 78% patients out of 100 belonged to rural areas which was also observed in a study by Bhal, et al.[17] Majority (55%) of our patients were categorized into WHO stage III (characterized by full blown AIDS and opportunistic infection) at the time of diagnosis whereas only 4% were detected to be in asymptomatic stage I. Heterosexual contact was the commonest route (94%) of transmission in this study which correlated well with the findings of NACO and studies of Indian observers like Mohanty, et al, Rajsekaran, et al.[15,18,19] General examination of the cases in this study established that 68% showed pallor as the most common clinical sign followed by lymphadenopathy, pedal oedema, cyanosis and skin rash in 18%, 6%, 4% and 4% respectively which is again consistent with the study by Agarwal SK, et al.[20] The mean TLC in this study was 5872±2210 cells per mm³ and it varied between 2000 to 10,200 cells per mm³ and 40% of them were leucopenic which is higher as compared to the earlier studies by Amballi, et al, and Amanda et al, due to the fact that in this study diagnosis of HIV infection was made in an advanced WHO stage III of AIDS.[21,22] The mean neutrophil count was 54±12.6% in this study and 29% were neutropenic out of which 18 were in stage III and IV and 11 were in stage I. But Amballi, et al found 42.4% of HIV infected with

neutropenia at the time of diagnosis and Zon and Groopman noted 13% neutropenic HIV infected cases in asymptomatic stage and 44% neutropenic in frank CDC-defined AIDS.[9,21] Thus, it is clear that in this study, more cases were in advanced stages of AIDS as because majority belonged to rural background with minimal awareness about the disease. Our study (with 67% in advanced stage) showed 30% cases with lymphopenia and CD4 count <200 cells per microlitre in 87% of the patients which is in accordance with WHO document and clinical staging of AIDS for adults and adolescents which ascertained both lymphocytopenia and fall in CD4 counts in AIDS.[23] Thus with a p value <0.05, correlation between lymphocytopenia and CD4 counts was found to be significant in this study. Thrombocytopenia was found in 41% patients with 38% (i.e. 27 of 67) and 42% (i.e. 14 of 33) of patients in advanced and asymptomatic stage respectively. Hence from our study it was clear that thrombocytopenia is seen in early and late stages of AIDS as was corroborated in earlier studies by Khandekar et al, Pechere et al, and Murphy et al.[13,24,25] The mean haemoglobin level in this study was 11.4±1.36gm/dl and ranged between 9g/dl to 14g/dl. In this study 79 patients had anaemia out of which 55 were males and 24 were females which was also earlier reflected in the studies by Amballi, et al, Ogun, et al and Zon et al.[9,21,26] Anaemia is an independent predictor of survival in HIV infected as mortality is high in anaemic HIV patients with CD4 <200 cells per microlitre thus highlighting the possibility of increased mortality in this set of patients. In addition to that, the present study shows occurrence of NNA in 56% cases which is less that the percentage seen in Erhabor, et al, and Patwardhan et al, in which NNA was present in 64% and 61% cases respectively.[27,28] Though the ESR was elevated in 71% of our patients it is neither sensitive nor specific as it is raised in almost all chronic infections. Our study also reflected that the analysis of associations between WHO staging of AIDS and other was not statistically significant but in contrast the correlation between anaemia and WHO staging was found to be significant. The incidence of anaemia was 75% in stage II, 87% in stage III and 75% in stage IV in this study thus proving that anaemia is higher in advanced stages as was earlier shown in the studies by Sullivan, et al.[10]

Authors noted in this study that among the patients with CD4 counts <200 cells per microlitre (i.e. 87% cases), 70% were anaemic, 36% had leucopenia, 26% had neutropenia, 30% had lymphocytopenia, 17% had monocytopenia and 35% had thrombocytopenia and similarly in patients with CD4 counts>200 cells per microlitre, 9% had anaemia, 4% had leucopenia, 3% had neutropenia, none had lymphopenia, 6% had thrombocytopenia and 3% had monocytopenia. Hence, it is evident that the occurrence of cytopenias increased with the progression of the disease. But the correlation between haemoglobin levels, ESR, TLC, DLC, platelet count with CD4 count was found to be insignificant in this study which is contrary to the studies by Suresh

Venkata Satya, et al and Gil Cunha de Santis, et al on 470 and 701 HIV infected patients respectively.[29,30] This is due to the fact that we had fewer cases in this study and didn't include patients on ARV therapy.

CONCLUSION

Detailed assessment of various haematological aspects of treatment naïve HIV infected patients and their statistical correlation with CD4 counts was not properly highlighted in any of the previous studies. In this study, authors could establish clear correlation between WHO staging of AIDS and haematological abnormalities and so also lymphocytopenia and CD4 counts. This study will be a guiding force in the future to evaluate AIDS patients explicitly on haematological basis and providing them with effective treatment to help them lead a better life.

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