Original Article

Can ferritin be a surrogate marker for CD4 cells in human immunodeficiency virus patients? A cross-sectional study of association of serum ferritin levels with immunological staging of human immunodeficiency virus patients

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Abstract

Introduction: The human immunodeficiency virus (HIV)/AIDS in India came into public view in 1986 with the detection of the first case of HIV in Chennai, Tamil Nadu, and the first AIDS case in Mumbai, Maharashtra in 1987. In acute phase response, iron distribution occurs in the liver and mononuclear phagocytic system. A high prevalence of elevated serum ferritin levels is reported in HIV infection and serum ferritin levels increase with the clinical worsening of infection and with decreasing CD4 lymphocyte counts. This study is designed to find the role of acute phase reactant serum ferritin in the progression of the disease of HIV which is complicated by opportunistic infections, by finding the correlation of serum ferritin with immunological stages of HIV. **Materials and Methods:** This cross-sectional study was conducted on 75 patients admitted to various wards of the Department of Medicine or attending medicine outdoor or ART Centre, Maharana Bhupal Government Hospital, RNT Medical College Udaipur. Serum ferritin, total iron binding capacity, and total serum iron were analyzed in Cobas® analyzer. CD4 cells are measured using the flow cytometry technique. The results were tabulated and subjected to statistical analysis. **Results and Conclusion:** There was a negative correlation among serum ferritin and CD4 cells with $r = -0.195$ which was statistically significant ($P < 0.05$). As the CD4 cell count decreased incidence of serum ferritin increased. Elevation of serum ferritin levels is associated with a low count of the CD4+ in HIV-diagnosed patients. In a patient diagnosed with HIV, elevated serum ferritin indicates underlying inflammatory pathology. Serum ferritin can be used as a guide to further evaluation of underlying disease in HIV patients.

Key words: AIDS, CD4 cells, ferritin, human immunodeficiency virus, immunology

Introduction

Human immunodeficiency virus (HIV)/AIDS has had a devastating impact on global health in recent times. Two different types of HIV, HIV-1, and HIV-2, affect humans. Considerable evidence exists favoring the hypothesis that HIV-1 in humans arose from cross-species transmission of an agent in chimpanzees, and HIV-2 from cross-species transmission from sooty mangabeys.[1-3]

CD4+ T lymphocytes are the principal targets of HIV. HIV infection causes both quantitative and qualitative defects in CD4+ T lymphocytes. Vital cells in the human immune system such as helper T-cells, macrophages, and dendritic cells are infected by HIV.[4]

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CD4+ T-cell plays an important role in assessing the prognosis of an HIV patient. CD4 count determination is recommended by all guidelines of HIV management and essentially all patients diagnosed with HIV infection have the results of this test available in their medical records.

Ferritin is a 24-subunit evolutionarily conserved protein. It functions to store the iron within the cytosol.[5] In certain clinical settings, ferritin levels can rise out of proportion

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to iron stores, reflecting its acute phase reactant properties, resulting from increased apoferritin (or L ferritin) synthesis and secretion, and increased ferritin release from injured cells.[6]

A high prevalence of elevated serum ferritin levels is reported in HIV infection and serum ferritin levels increase with the clinical worsening of infection and with decreasing CD4 lymphocyte counts.[7]

This study is designed to find the role of acute phase reactant serum ferritin in the progression of the disease of HIV which is complicated by opportunistic infections, by finding the correlation of serum ferritin with immunological stages [Table 1][8] of HIV.

Materials and Methods

This present cross-sectional study was conducted on 75 patients admitted to various wards of the Department of Medicine or attending medicine outdoor or ART Centre, Maharana Bhupal Government Hospital, RNT Medical College Udaipur.

Inclusion criteria

1. All newly diagnosed and previously diagnosed patients of >18 years of age and either sex proved to be HIV positive.

Exclusion criteria

1. Age <18 years
2. Pregnant females
3. Patients on hematinics
4. Congenital hematological disorder.

Parameters for assessment

Complete blood count (hemoglobin, total and differential leukocyte count, and platelet count), serum ferritin, total iron binding capacity, and total serum iron were done along with CD4 cell count. Serum ferritin, total iron binding capacity, and total serum iron were analyzed in Cobas® analyzer. CD4 cells are measured using flow cytometry technique. A biological reference value for the iron profile is as follows:

- Serum Iron = 33.00–193.00 µg/dl
- TIBC = 250.00–450.00 µg/dl
- Serum ferritin = 22.00-322.00 ng/ml.

Statistical analysis

The results were tabulated and subjected to statistical analysis. Statistical tests used included analysis of variance and Spearman correlation. The data were entered into Microsoft Office 2013 Excel worksheet and statistical analysis was done using SPSS (SPSS Inc. Released 2004. SPSS for Windows, Version 12.0. Chicago, SPSS Inc). Descriptive statistics were applied; $P < 0.05$ was considered statistically significant.

Results

We conducted this study on a total of 75 of HIV-infected patients. Among them, 34 patients were female and 41 patients were male. In this study, 34 (45.33%) of the study population belonged to female sex and 41 (54.67%) belonged to male sex.

We classified the study population into three stages as per the CDC immunological staging of HIV patients based on CD4 cell counts.[8] Table 2 shows sex distribution and immunological staging of the study population. Out of 28 patients in Stage 1, 13 (46.43%) were females and 15 (53.57%) were male patients. Out of 35 patients in Stage 2, 18 (51.43%) were female and 17 (48.57%) were male patients. Out of 12 patients in Stage 3, 3 (25%) were female and 9 (75%) were male patients.

Table 3 shows distribution of study population as per the centers for disease control immunological staging based on CD4 cell count. In our study on 75 patients, 28 patients were in Stage 1 with CD4 count of more than 500/µl. Out of 28 patients, 12 (42.86%) patients had below normal serum ferritin value, 15 (53.57%) patients had normal serum ferritin value, and 1 (3.57%) patient had serum ferritin above normal range.

Out of 35 patients, who were in immunological Stage 2 with CD4 counts value of 200–500/µl, 18 (51.43%) patients had serum ferritin less than normal value, 15 (42.86%) patients had normal serum ferritin value, and 2 (5.71%) patients had serum ferritin value above normal range.

Tweleve patients had CD4 counts <200/µl and 2 (16.67%) of them had serum ferritin value below normal range, 5 (41.67%) patients had serum ferritin value in normal range, and 5 (41.67%) patients had serum ferritin value above normal value.

Discussion

In our study, we also compared the association of serum ferritin with immunological staging of HIV patients based on CD4 counts.[8] 46.67% patients of in the study group had serum ferritin in the normal range. Among the patients with Stage 3 of immunological staging, 41.67% of the patients had serum ferritin value more than the normal range. Only 16.67% of the patients who belonged to Stage 3 had serum ferritin value below normal value. Among the patients who belonged to Stage 1 of immunological staging, only 3.57% had serum ferritin value above the normal range. These values were statistically significant ($P = 0.03$) [Table 4].

Table 1: Immunological staging of human immunodeficiency virus in the human immunodeficiency virus infected individual above age 6 years[8]

HIV infection Stages 1-3 based on age-specific CD4+ T lymphocyte count	
Stage	Cells/µL
1	>500
2	200-499
3	<200

HIV=Human immunodeficiency virus

Table 2: Immunological staging and sex distribution

Immunological stage	Female, *n* (%)	Male, *n* (%)	Total, *n* (%)
1 (CD4 >500)	13 (46.43)	15 (53.57)	28 (100.00)
2 (CD4 200-499)	18 (51.43)	17 (48.57)	35 (100.00)
3 (CD4 <200)	3 (25.00)	9 (75.00)	12 (100.00)
Grand total	34 (45.33)	41 (54.67)	75 (100.00)

Table 3: Distribution of study population as per the CDC (centers for disease control) immunological staging based on CD4 cell count

Immunological staging	*n* (%)
1	28 (37.33)
2	35 (46.67)
3	12 (16.00)
Total	75 (100)

CDC=Centers for disease control

Table 4: Correlation between serum ferritin and immunological staging of human immunodeficiency virus patients based on CD4 counts

Serum ferritin (nanogram/dL)	Immunological stage			
	1, *n* (%)	2, *n* (%)	3, *n* (%)	Total, *n* (%)
<22	12 (42.86)	18 (51.43)	2 (16.67)	32 (42.67)
22-322	15 (53.57)	15 (42.86)	5 (41.67)	35 (46.67)
>322	1 (3.57)	2 (5.71)	5 (41.67)	8 (10.67)
Total	28 (100.00)	35 (100.00)	12 (100.00)	75 (100.00)

Serum ferritin was plotted against CD4 cell counts [Figure 1]. There was a negative correlation among these two variables with $r = -0.195$ which was statistically significant ($P < 0.05$). HIV infection leads to low levels of CD4+ T-cells through three main mechanisms: First, direct viral killing of infected cells; second, increased rates of apoptosis in infected cells; third, killing of infected CD4+ T-cells by CD8 cytotoxic lymphocytes that recognize infected cells.[4] As the CD4 cell count decreased incidence of serum ferritin increased. With good compliance to antiretroviral therapy, patients are known to have increased CD4 cell counts.[9] The role of serum ferritin as an indicator of good compliance with antiretroviral therapy can be considered with this result.

Kumar *et al*. noted hyperferritinemia was correlated with immunological staging of the disease. There was significant association was found ($r = 0.890$). As the disease advanced higher levels of ferritin were noted.[7]

Saragih *et al*. found that there was a significance between the serum ferritin levels with the CD4+ cell count. They showed that the lower the CD4+ value due to the progressivity of the HIV disease, the higher the serum ferritin. Conversely, the higher value of CD4+, the lower the serum ferritin.[10]

A multi-country analysis research conducted by Namaste *et al*. showed concern about how ferritin concentration should adjust in inflammation disease. They found a significant correlation between ferritin and C-reactive protein (CRP) serum. The ferritin serum was found highest when the CRP serum was elevated. This supports the results from a study conducted in critical care in a hospital in the USA where they found that ferritin serum was higher in a group of people diagnosed with hemophagocytic lymphohistiocytosis (HLH), a disease where there is an overactive reaction of macrophage and lymphocytes, including an increase in the CRP serum. The study determined that the cut-off point of serum ferritin in diagnosing HLH will help clinicians to make an immediate diagnosis and later better management. These studies showed us that serum ferritin and diseases producing inflammation are highly related.[11]

Thus, serum ferritin levels may prove to be a useful marker to monitor disease progression.

Conclusion

Elevation of serum ferritin levels is associated with a low count of the CD4+ in HIV-diagnosed patients. In a patient diagnosed with HIV, elevated serum ferritin indicates underlying inflammatory pathology. Serum ferritin can be used as a guide for further evaluation of underlying disease in HIV patients. Clinicians should make serum ferritin levels one of the concerns in the progressivity of the disease to have better management. In addition, serum ferritin should be used cautiously while assessing the iron status of the HIV-infected patients. Further studies are needed with a larger study population with more variety in the characteristics of the study population.

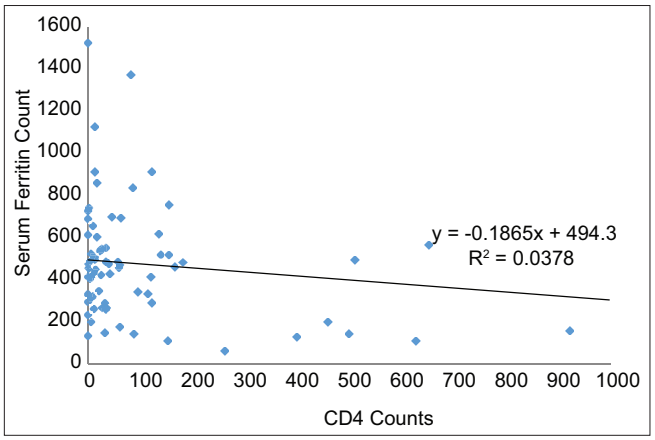

Figure 1: Shows the graphical representation of serum ferritin and CD4 cell counts. There was a negative correlation among these two variables with $r = -0.195$ which was statistically significant ($P < 0.05$)

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Conflicts of interest

There are no conflicts of interest.

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