

PREVALENCE OF HIGH SERUM AND RED CELL FERRITIN LEVELS IN HIV-INFECTED PATIENTS

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ABSTRACT

We report a high prevalence of elevated serum and red cell ferritin (SF and RCF) levels in 168 patients with HIV infection. SF levels increase with clinical worsening of infection and with decreasing CD4⁺ lymphocyte counts (ANOVA, $p < 0.001$) while RCF is significantly higher in asymptomatic AIDS patients (ANOVA, $p < 0.001$) and in those treated with zidovudine (AZT) (ANOVA, $p < 0.001$). It is suggested that, although inflammatory processes may explain high SF levels, if we also take in account RCF levels a possible association between iron overload and HIV infection might exist, and this may be worsened by AZT treatment. The significance of these high ferritin levels and their effects on immune system suppression and susceptibility to infectious and neoplastic complications in these patients merits further investigation.

Key words: HIV, red cell-ferritin, serum-ferritin, zidovudine

B lumberg et al. in 1984¹ and other authors subsequently^{2,3} reported high serum ferritin levels in human immunodeficiency virus (HIV)-infected patients. It has also been observed that ferritin levels increased as the disease progressed.^{4,5} Some authors suggest that ferritin, which is known to inhibit T-cell functions and proliferation, might play a certain role in the cell-mediated immunodeficiency observed in AIDS.⁶

We evaluated liver type serum ferritin (SF) and red cell ferritin (RCF) in a series of 168 consecutive randomly selected patients with HIV infection. Clinical characteristics of the subjects are shown in Table 1. Neither SF nor RCF levels differed from the controls in 60 patients (36%). However, SF was increased in 44 (26%), both SF and RCF were increased in 33 (19.6%) and only RCF was raised in 21 patients (12.5%). The concentrations of each ferritin were more than twice the upper physio-

logical level in 54% of the 77 patients with raised SF and in 68% of the 54 patients with raised RCF. Low SF with a physiological RCF level was detected in 9 patients (5.3%). Conversely, a physiological SF level with decreased RCF was observed in only one patient (0.6%).

On the basis of the clinical data and due to the close relationship existing between inflammatory processes and iron binding proteins, patients were distributed into three groups: asymptomatic HIV positive patients (group 1, $n=86$), asymptomatic patients who met the CDC criteria for AIDS (group 2, $n=22$) and AIDS patients with an acute complication requiring hospitalization (group 3, $n=60$). The accuracy of patients distribution in these three clinical groups was assessed in concomitance with CD4⁺ lymphocyte counts (Chi-square = 57.62, $p < 0.001$). Ferritin levels in each group are shown in Table 2. The highest mean SF level

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Table 1. Clinical characteristics of the 168 patients.

<i>Risk groups</i>		
Drug addicts	125	(74%)
Homosexuals	28	(17%)
Heterosexuals	10	(6%)
Others	5	(3%)
<i>Underlying disorders</i>		
Malnourishment or malabsorption disorders	14	(8%)
Bleeding disorders	5	(3%)
Neoplastic disorders	9	(5%)
Infectious disorders	74	(44%)
Liver disorders	73	(43%)
Alcohol abuse	69	(41%)
Hydrazide treatment	21	(12%)
AZT treatment	48	(29%)
Iron or transfusion therapy	5	(3%)
Other	13	(8%)

was found in group 3 and the lowest in group 1. The highest mean RCF levels were found in group 2.

Patients were also classified according to their CD4⁺ lymphocyte counts. We compared the ferritin levels of 109 patients with less than 300×10⁶/L CD4⁺ lymphocytes to those of the remaining 59 patients. Mean SF levels were higher in the former group, with a geometrical mean (G) of 330 μg/L and a confidence interval (CI) of 261-418 μg/L, than in the latter group (G = 86 μg/L, CI of 60-125 μg/L)(ANOVA p<0.001). The same observation was true concerning RCF levels which were higher in the former (G=481 μg/L of packed red cells, prc, CI of 392-591 μg/L prc) than in the latter (G=296 μg/L prc and CI of 221-396 μg/L prc)(ANOVA p<0.01).

Finally, we compared the ferritin levels of 48 patients on zidovudine (AZT) treatment with those of untreated patients. No differences were found in mean SF levels between treated (G=246 μg/L, CI of 165-365 μg/L) and untreated patients(G=196 μg/L, CI of 150-256 μg/L). However, mean RCF levels were significantly higher in the former (G=751 μg/L prc, CI of 524-1075 μg/L prc) than in the latter group (G=318 μg/L prc, CI of 268-378 μg/L prc) (ANOVA P<0.001).

Ferritin and iron overload have been linked to

a variety of immunosuppressive effects on cell-mediated immunity in vitro.⁷ We observed a high prevalence of increased SF levels in our patients and their gradual increase with progression of the disease and decrease of CD4⁺ lymphocyte counts. Inflammatory response itself may determine a nonspecific increase in SF.⁸ As expected, SF levels were higher in group 3 patients. On the other hand, we found a high prevalence of increased RCF levels, especially in patients of group 2. The cause and the significance of these high RCF levels are obscure. The raised RCF levels associated with high SF levels suggest iron overload, which increases the risk of infection.⁹ Hence, iron overload may contribute to worsen infectious complications in HIV-infected patients and to immunosuppression through inhibitory effects on cell-mediated immunity by ferritin. Moreover, we also observed that patients on AZT treatment presented higher mean RCF levels than did untreated ones. If AZT increases tissue iron, as is also suggested by Pollack et al.,¹⁰ that could have a detrimental effect on some of the infections in these patients.

Understanding the mechanisms of these ferritin alterations as well as their immunological and clinical significance in HIV-infected patients warrants more comprehensive laboratory and clinical studies on: 1) the possible association between HIV infection and hemochromatosis; 2) the immunosuppressive effects

Table 2. Clinical groups and ferritin levels.

Groups	SFT* (μg/L)	RCFT** (μg/L prc)
1 (n=86) 51%	112 (84-149)	320 (259-395)
2 (n=22) 13%	239 (146-391)	773 (432-1384)
3 (n=60) 36%	487 (354-671)	453 (341-603)
	ANOVA* p < 0.01	ANOVA° p < 0.001

*geometric mean and 95% confidence interval; †normal values 120-550 μg/L prc; #all three groups showed significant differences; °differences between

of ferritin on these patients and on their susceptibility to infection; 3) the effect of AZT therapy on iron metabolism, and 4) the potential role of ferritin as a marker protein in HIV infection.

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