

Research Article

Serum ferritin levels in human immunodeficiency virus infected children and its relation with severe immunodeficiency

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ABSTRACT

Background: Ferritin is an acute phase protein which is often elevated in acute and chronic inflammation. In adults with human immunodeficiency virus (HIV) infection, elevated serum ferritin levels indicate advanced or progressive disease. In the present study, ferritin levels were evaluated in HIV infected children to find out its relation with the immune deficiency.

Methods: The children who were HIV positive (confirmed by ELISA for HIV-1 and HIV-2), and attending the OPD of ART Centre and of tertiary care center during period of one year were included in the study. The study population consisted of 47 patients, belonging to both sexes and age of 18 months to 19 years. Detailed history was taken and full clinical examination done in all cases. Blood sample for Complete blood count, serum ferritin and CD4 count was taken. Absolute CD4 count of each patient was obtained and immunological staging was done on the basis of WHO immunological staging criteria. Serum ferritin level 7-140 ngm/mL was considered normal.

Results: Hyperferritinemia (>140 ngm/ mL) is a feature of advanced stages of HIV infection. 11.1% patients of stage 3 and 40.0% patients of stage 4 are showing hyperferritinemia ($r = 0.890$), irrespective of anemia. Low serum ferritin level (<7 ngm/mL) is an unusual feature in HIV infected children.

Conclusions: High Serum ferritin levels are not uncommon in children with HIV disease and they are related with immunological progression of the disease.

Keywords: HIV, Serum ferritin, CD4 count, Immunological stage

INTRODUCTION

Ferritin is a 24-subunit evolutionarily conserved protein. Within the cytosol, its main function is to store iron in a soluble nontoxic form, protecting the cell from iron-mediated oxidation-reduction reactions. In the circulation, it acts as a delivery mechanism, and serum levels usually reflect total body iron stores.¹ However, despite physiological regulation of iron homeostasis, the proportionality does not always hold true and a host of conditions have been implicated to cause markedly elevated serum ferritin levels.²⁻⁴ Interpretation of an

elevated serum ferritin value will vary significantly depending on the patient population and local epidemiology.^{2,3}

It can be abnormally elevated in a wide range of disease states including malignancy, infection, inflammation, and chronic iron-overload syndromes. Previous investigators have examined the underlying causes of markedly elevated ferritin levels. Liver disease, malignancy, and renal disease have been found to be prominent causes,² and infections predominated in a recent HIV-positive cohort.⁵

Hyperferritinaemia seems to be a common finding in HIV-1-positive population groups, with an estimated prevalence of 16-36%.^{2,6} Within this clinical context, infectious diseases are often cited as the most common cause for elevated serum ferritin.

In adults, high prevalence of elevated serum ferritin levels are reported in HIV infection and serum ferritin levels increases with clinical worsening of infection and with decreasing CD4+ lymphocyte counts. 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.⁷

Serum ferritin should be used cautiously to assess iron status in patients with advanced HIV infection.⁸

METHODS

Forty seven newly diagnosed HIV infected children, attending the OPD of ART Centre and OPD of SN Children Hospital, Allahabad, during period of one year from August 2008 to July 2009 were enrolled in the study. The children who were HIV positive (confirmed by ELISA for HIV-1 and HIV-2), and age of 18 months to 18 years were included in the study.

HIV positive patients who were taking hematinics or having history of blood transfusion or critically ill, were excluded from the study.

Ethical approval was obtained and written consent was taken from parents/guardian prior to investigation. Detailed history was taken and full clinical examination done in all cases. Parents and sibling's HIV infection status was also enquired. Complete physical examination was done to assess clinical state of the patient. Absolute CD4 count was done with Partec CyFlow® counter flow cytometer. CD4 count is used to assess the immunological status of the HIV infected child.

Serum ferritin

Ferritin is a high-molecular-weight ferrous protein with its main function being iron storage. Serum ferritin levels usually reflects total body iron stores, since its secretion into circulation is proportional to the amount of cellular iron in the form of cellular ferritin.⁹

Serum ferritin was measured with IMMULITE®1000 SYSTEM-two site chemiluminescent immunometric assay. 10 µL of centrifuged serum was taken in test tube. Ferritin reagent wedge used in system contains alkaline phosphatase (Bovine calf intestine) conjugated to polyclonal goat anti-ferritin in buffer with sodium azide as preservative. Serum ferritin level 7 to 140 ngm/mL in pediatric age group (6 months to 15 years) is taken as normal.¹⁰

Data analysis

Data was analyzed using SPSS software. To describe nominal data, simple percentages were used. Mean and standard deviations were used to describe normally distributed data from the subjects. The Spearman rank correlation test was used to determine the relationship between different continuous variables.

RESULTS

In total 47 patients were enrolled in the study. The age distribution for the entire study population varied from 18 months to 14 years, with a mean of 6.64 years (SD 3.59 years).

Table 1: Distribution of cases by age and sex.

Age group	Male (%)	Female (%)	Total (%)
1.5-5 year	18 (38.30)	4 (8.51)	22 (46.81)
5-10 year	13 (27.66)	4 (8.51)	17 (36.17)
10-15 year	6 (12.77)	2 (4.25)	8 (17.02)
Total	37 (78.73)	10 (21.27)	47 (100)

Out of 47 patients, 37 (78.7%) were male and 10 (21.3%) were female with overall male to female ratio 3.7:1. The most commonly involved age group was 1.5-5 years. Almost half (46.81%) of cases belongs to this group. As the age increased, the number of cases found to be decreased. There was no case in age group 15-18 years (Table 1).

Table 2: Immunological staging.

Immunological staging	Number of patients	Percentage
Stage 1	24	51.06
Stage 2	9	19.15
Stage 3	9	19.15
Stage 4	5	10.63
Total	47	100.0

Absolute CD4 count of each patient was obtained and immunological staging was done in every case on the basis of WHO immunological staging criteria. Out of 47 cases, 24 (51.06%) cases were found in stage 1 of the disease, 9 (19.15%) cases each in stage 2 and 3 while rest of the 5 (10.63%) cases were found in stage 4 (Table 2).

The mean serum ferritin level in our study was 47.79 ngm/mL which range from 1.89 to 439.0 ngm/mL (SD 68.04 ngm/mL). It was low (<7 ngm/mL) in 10 (10.6%) and elevated (>140 ngm/mL) in 3 (6.4%) cases only (Table 3).

Table 3 depicts that normal value of serum ferritin may found in every stage of the disease while hyperferritinemia (>140 ngm/mL) is a feature of advanced stages of HIV infection. 11.1% patients of stage

3 and 40.0% patients of stage 4 are showing hyperferritinemia, irrespective of anemia. Observations in the above mentioned table are statistically significant

(p value = 0.013 which is <0.05). Low serum ferritin level (<7 ngm/mL) was an unusual feature in HIV infected children.

Table 3: Distribution of serum ferritin levels in relation to immunological staging.

Serum ferritin levels	Immunological stages				Total	$\chi^2 = 16.135$ DF = 6 p = 0.013 (<0.05)
	Stage 1	Stage 2	Stage 3	Stage 4		
<7 ngm/mL	1 4.2%	2 22.2%	2 22.2%	0 0.0%	5 10.6%	
7-140 ngm/mL	23 95.8%	7 77.8%	6 66.7%	3 60.0%	39 83.0%	
>140 ngm/mL	0 0.0%	0 0.0%	1 11.1%	2 40.0%	3 6.4%	
Total	24 100.0%	9 100.0%	9 100.0%	5 100.0%	47 100.0%	

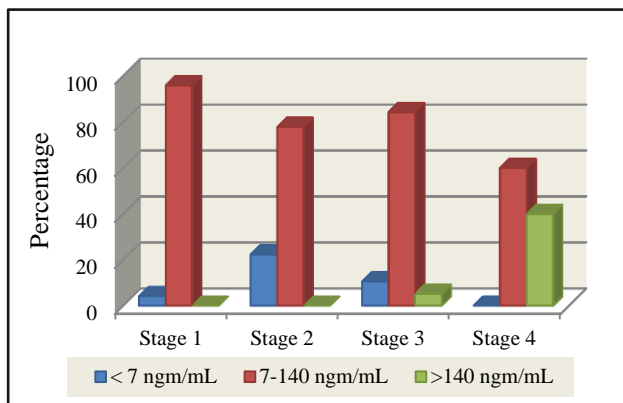


Figure 1: Distribution of serum ferritin levels in relation to immunological staging.

DISCUSSION

Serum ferritin level is a nonspecific indicator of systemic illness and widely accepted as an acute-phase reactant and is nonspecifically elevated in a wide variety of inflammatory states including infection, malignancy, and autoimmune diseases. Serum ferritin can be elevated through a variety of mechanisms, which may overlap or coexist. Systemic inflammation plays a key role in the initiation and perpetuation of hyperferritinaemia.

In our study, we reported normal serum ferritin levels in most of the patients (83%) and these normal levels of serum ferritin were distributed in all stages of the disease. But these normal levels of serum ferritin were more prevalent in early stages of the disease as compare to late stage. The overall prevalence of high serum ferritin levels was 6.38% in our study. Calderon CL et al.¹¹ reported hyperferritinaemia in 11% of cases in a study conducted on adult HIV positive patients and Ellaurie M et al.¹² reported even higher prevalence. The possible cause for

low prevalence of hyperferritinaemia in this study is that, most of the sick patients of advance staging are not included in the study due to exclusion criteria. Unfortunately, no more studies on pediatric population are available.

When the hyperferritinaemia was correlated with immunological staging of the disease, a significant association was found ($r = 0.890$), it means as the disease advanced (stage 3 and 4), the higher levels of the serum ferritin were noted. Ellaurie M et al.¹² reported that increasing levels always accompanied or closely preceded rapid disease progression. Ellen James et al.¹³ demonstrated that hyperferritinemia may occur with iron deficiency in HIV infected children. According to Salhi Y et al.,¹⁴ patients with higher ferritin level entered stage 4 more rapidly than those with a lower level. The ferritin level was found to be an independent predictor of progression of HIV disease. Thus, serum ferritin levels may prove to be a useful marker to monitor disease progression.

In conclusion, although normal serum ferritin level may occur in any stage of the disease, but the elevated ferritin levels are associated with advanced stages of the disease. In addition, serum ferritin should be used cautiously to assess iron status in patients with advanced HIV infection.

Key messages

The high serum ferritin levels are associated with immunological progression of the disease.

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Ethical approval: The study was approved by the institutional ethics committee

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