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*Original Article*

# Ferritin as an indicator of disease activity in Hodgkin lymphoma in pediatric patients

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**Abstract:** Introduction: Hodgkin lymphoma is a malignant proliferation of lymphatic system which when advanced can involve the bone marrow. It is usually indolent and responds to chemotherapy. However the prediction of rapidly progressive disease is often dependent on lot of clinicopathological parameters. Serum ferritin may act as a marker for disease activity in these patients. But the prior studies have failed to establish its role or group the patients into prognostic categories. Aims: To study the status of serum ferritin at time of admission and after completion of chemotherapy and also iron overload induced organ involvement in the form of hepatic, cardiovascular and thyroid dysfunction in nine patients admitted in our ward with Hodgkin lymphoma and receiving treatment in the form of chemotherapy. Methodology: A spectrum of clinicopathological variables were tested at baseline and after treatment liver function test, thyroid function test, 2D echocardiography, Ultrasound abdomen, PET scan and serum ferritin level. Conclusion: Serum ferritin at baseline statistically correlated with disease activity however the final ferritin values reduced to significant values in patient that underwent remission, and hence grouping of patients based on serum ferritin values can serve as better outcome predictors. Although transfusion requirement was very rare in the patients the levels of serum ferritin correlated with disease activity. Serum ferritin level may act as a predictor of disease activity and remission.

**Keywords:** Serum ferritin, Hodgkin's lymphoma, prognosis, disease progression

## Introduction

Hodgkin lymphoma is a monoclonal proliferation of the B cell lineage leading to lymphadenopathy at various sites with a histological hall mark of Reed sternberg cells. Although amenable to cure with chemotherapy and having a 5 year survival rate of approximately 90%. A late presentation or relapse may be fatal with need for intensive chemoradiotherapy and significant adverse effects. Patients usually have a bimodal peak of presentation with upto 50% presenting in advance stages 3 and 4. In the past it has been studied that there is correlation of high ferritinemia with severity of presentation in Hodgkin lymphoma. In a study from Spain 5 year progression free survival was relatively lesser in Presentation with ferritin level above 350 microgram/L as low as 69% where as it was as high as 89% in those with lower ferritin level [1].

A study from Germany conducted on patients aged 15 to 61 revealed increaser in ferritin level with increase in disease stage along with median ferritin level reaching up to 311 microgram/l in stage 4 and a *P* value <0.0001 between difference of ferritin level in remission and progression [2]. A few isolated hospital based studies have also highlighted the importance of ferritin in prognostication of Hodgkin's disease, however the role in the disease remission was never correlated [3-5]. Ferritin is an acute phase reactant which is increased in most stress situations such as fever and even malignancies like leukemia and lymphoma. Ferritin is frequently elevated in children receiving frequent blood transfusion as iron scavenged by macrophage after destruction of heme molecule is stored in form of ferritin. In cases of advanced stage Hodgkin lymphoma which may require frequent blood transfusion ferritin can

be significantly high due to both disease process as well as multiple blood transfusion. Here we present a series of 9 cases of advanced cases of Hodgkin lymphoma where post treatment ferritin level is significantly lower than pre-treatment level and statistically correlated with outcomes.

## Materials and methods

An observational study at patients with histopathological diagnosis of Hodgkin's disease was conducted after due ethical consideration. The patient selection criteria are as follows.

*Inclusion criteria*

1. Patient age on presentation 1 to 12 years. 2. A histopathological diagnosis of Hodgkin's disease. 3. Consent by patient/guardian/next of kin for inclusion in study.

*Exclusion criteria*

1. History of prior chemotherapy or radiotherapy. 2. History of pre-existing organ dysfunction. 3. Consent not given for participation in study.

Nine patients with diagnosed advanced stage Hodgkin lymphoma were enrolled and there baseline liver function test, ferritin level, Ultrasound of liver and 2D-echo were performed before starting treatment and these parameters were re-evaluated after completion of 6 cycles of ABVD.

The baseline parameters were tested as per clinical protocol. FDG-PET was done to review disease activity. The organ dysfunction studied included the hepatic and cardiac dysfunction.

Hepatic Dysfunction was assessed as per the child Pugh's clinical score:

- Encephalopathy: None =1 point, Grade 1 and 2=2 points, Grade 3 and 4=3 points.
- Ascites: None =1 point, slight =2 points, moderate =3 points.
- Bilirubin: under 2 mg/ml =1 point, 2 to 3 mg/ml =2 points, over 3 mg/ml =3 points.
- Albumin: greater than 3.5 mg/ml =1 point, 2.8 to 3.5 mg/ml =2 points, less than 2.8 mg/ml =3 points.
- Prothrombin Time* (sec prolonged): less than 4 sec =1 point, 4 to 6 sec =2 points, over 6 sec =3 points.

*Frequently INR will be used as a substitute for PT, with INR under 1.7=1 point, INR 1.7 to 2.2=2 points, INR above 2.2=3 points.

The severity of cirrhosis:

- Child-Pugh A: 5 to 6 points.
- Child-Pugh B: 7 to 9 points.
- Child-Pugh C: 10 to 15 points [6].

The cardiac dysfunction was assessed as per NCI criteria laid down.

Proposes the Common Terminology Criteria for Adverse Events (CTCAE) that define left ventricular dysfunction and HF based on severity into grades 1 to 5.

1. Grade 1 is asymptomatic elevations in biomarkers or abnormalities on imaging. 2. Grades 2 and 3 consist of symptoms with mild and moderate exertion. 3. Grade 4 includes severe, life-threatening symptoms requiring hemodynamic support. 4. Grade 5 involves death [7].

Blood transfusion is a confounding factor of raised ferritin level for TRIO immediately after BT. (Transfusion related iron overload) and these values were excluded from study. A repeat testing after 21 days were done for these patients.

Disease activity and remission status was evaluated using FDG-PET scan. Cardiovascular function was observed in the form of 2 echocardio-graphic measurements, E/A ratio for diastolic dysfunction and EF or ejection fraction for systolic dysfunction. Liver function was analyzed biochemically by serum Bilirubin, SGOT and SGPT level and also by ultrasonography. Number of blood or packed cell transfused prior to starting of treatment and during course of treatment was also recorded. The prognostic grouping of ferritin values were done by paired T test. The values of ferritin were considered significant if $P$ value was $<0.05$ in each group. The SPSS software version 13 was used for analysis of all statistical values. The final ferritin values after 4/6 cycles of ABVD were considered for disease activity indicator. The

patients were grouped into 3 categories based on outcome values.

## Results

All 9 patients had advanced Hodgkin lymphoma. FGD-PET was done at start of treatment and after 4 cycles of ABVD. All children except one received 6 cycles of ABVD with radiotherapy for those with bulky disease. One child died during course of treatment due to septic shock.

Out of 9 children 3 had complete remission, 1 after 4 cycles of ABVD and 2 after 6 cycles of ABVD. The disease stage, organ dysfunction and ferritin level is shown in **Table 1**. Five of 9 had partial remission 3 of whom had bulky disease and received radiotherapy. All of the children received ABVD cycles barring one who had initial raised Bilirubin level and was given 1 cycle of CHOP and then ABVD was introduced.

The children were grouped into mild, moderate and sever ferritin values [Mild elevation-Serum Ferritin less than 500 ng/ml, Moderate elevation-Serum ferritin 500-1000 ng/ml, severe ferritin elevation-Serum ferritin >1000 ng/ml]. The patients were grouped into 3 categories based on outcome values. The results are discussed in **Table 2**. The outcome in general was good for stage III disease, indicating clinical stage is an independent prognostic factor. However patients with elevated serum ferritin either moderate or severe lead to more partial remission states versus low serum ferritin levels. The results are however limited by the small sample size. The study needs more validation with larger samples. After 4/6 cycles of ABVD the reduction in ferritin was correlated with the remission status. It was high in non-responders and low in responders.

Serum ferritin initial level was high in 8 out of 9 children of whom only 3 had ever received any blood transfusion. Cardiovascular function was essentially normal in all the children before and after treatment whereas mild derangement of liver function present initially in 2 out of 9 children was normalized after treatment. Mean serum ferritin was 623 microgram/l before treatment which reduced to 339 microgram/l after treatment completion and it was found statistically significant by student T test. For a alpha of 0.05 the paired critical t was +1.2. Correlation study showed no significant correlation of the number of transfusion received with the ferritin level. ANOVA test was conducted for serum ferritin values of patients with complete remission against the group with partial remission and an F value of 0.48 was obtained for an alpha of 0.05. The same when done after therapy showed an F value of 0.74 in favor of having lower ferritin level in those with complete remission which was statistically significant.

Serum ferritin level was reduced after treatment in all cases and it was found statistically significant by student T test expect one child who expired required 4 blood transfusion during ABVD cycles and had very high serum ferritin level after 6 courses despite having near normal liver function and normal cardiac function indicating serum ferritin in this case was not related to iron overload induced organ dysfunction. Therefore disease activity status seemed to correlate more with the ferritin level. The study however has some shortcomings, serial monitoring of serum ferritin levels could identify trend of disease course better as compared to values at diagnosis and at outcomes. Also a lower sample size limits the significance and power of inferences, a larger study with big sample size is needed to clinically validate our findings.

## Discussion

Abnormally high serum ferritin level is associated with leukemia and lymphomas [1]. It functions as a prognostic factor for NHL [2]. Tissue of Hodgkin disease has various antigens some of which are specific for the disease but some are nonspecific. The study by Eshgar Order and Katz in 1974 showed the presence of ferritin in high amount in tissue of Hodgkin lymphoma which was biochemically and immunologically similar in characteristic to ferritin isolated from liver and was considered as an oncofoetal antigen [3]. Study by Jacobs an Slater showed presence of high ferritinemia in untreated adult Hodgkin disease as well as increase in level with advancing stages and a study by biebar on adult Hodgkin disease showed 44% chance of high ferritin level [4]. Hann et al. showed ferritin and transferring to be potent prognostic factor for progression free survival in Hodgkin disease [5], where they found ferritin and transferring level to be inversely related and with advancement of stages ferritin level increased and transferrin level lowered. Ferritin level increas-

**Table 1.** Before and after treatment, organ dysfunction, remission status and Ferritin level in children with Hodgkin lymphoma

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Age in years | 5 | 5 | 12 | 10 | 7 | 12 | 12 | 8 | 10 |
| Gender | Male | Male | Male | Male | Male | Male | Female | Male | Male |
| Stage | Stage 4 bulky | Stage 4 bulky | Stage 3 | Stage 4 bulky | Stage 4 | Recurrence of disease after 4 year event free | Stage 4 Bulky | Stage 3 | Stage 4 |
| Number of transfusion before treatment | 4 | 1 | Nil | Nil | Nil | 4 | Nil | Nil | 3 |
| Baseline ferritin (ng/ml) | 1445.4 | 1500 | 19.5 | 539.6 | 279.8 | 355.3 | 260.5 | 936.8 | 269.7 |
| Baseline 2D Echo EF | 69.7% | 70% | 68.2% | 71.5% | 64% | 60% | 63.9% | 61% | 54.7% |
| Baseline 2D Echo E/A | 1.3 | 1.4 | 1.6 | 1.2 | 1.1 | 1.3 | 1.6 | 1.5 | 1.8 |
| Baseline SGOT/SGPT | 119/159 | 57/70 | 30/10 | 24/10 | 39/21 | 22/43 | 14/13 | 45/68 | 25/42 |
| Baseline total serum bilirubin | 0.6 | 1.7 | 0.3 | 0.5 | 0.1 | 0.8 | 0.6 | 1.1 | 0.5 |
| Baseline liver echotexture USG | NAD | NAD | NAD | NAD | NAD | NAD | NAD | NAD | NAD |
| Number of blood transfused during treatment | 1 | Nil | Nil | Nil | 4 | 2 | Nil | Nil | Nil |
| Final ferritin (ng/ml) | 178.1 | 539.1 | 11.5 | 1650 | 8.5 | 299.9 | 44.5 | 61.3 | 262.9 |
| Final 2D ECHO EF | 69% | 67% | 67.2% | 73.6% | 70% | 67% | 64% | 62.3% | 62% |
| Final 2D Echo E/A | 1.6 | 1.8 | 1.7 | 1.3 | 1.3 | 1.6 | 1.7 | 1.4 | 1.6 |
| Final SGOT/SGPT | 47/42 | 33/30 | 28/44 | 102/114 | 47/25 | 59/78 | 28/33 | 32/41 | 28/30 |
| Final total serum bilirubin | 0.5 | 0.7 | 0.5 | 1.4 | 0.2 | 0.5 | 0.4 | 0.7 | 0.8 |
| Final liver echo-texture USG | NAD | NAD | NAD | NAD | NAD | NAD | NAD | NAD | NAD |
| Status after 6 cycles of ABVD | Partial remission | Partial remission | Complete remission | Died | Completion | Partial remission | Partial remission | Complete remission | Partial remission |

ABVD, doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine; USG, ultrasonogram; 2D ECHO, 2D echocardiography; SGOT, serum glutamic-oxaloacetic transaminase, or AST; SGPT, Serum glutamic pyruvic transaminase or ALT.

**Table 2.** Correlation of ferritin and grouping into prognostic categories with outcome variables

| S No | Category of serum ferritin | Stage of clinical disease | No of patients | Complete remission | Partial remission | *P* value |
|---|---|---|---|---|---|---|
| 1 | Serum Ferritin less than 500 ng/ml | Stage 3 | 1 | 1 (100%) | 0 | 1.2 |
| | | Stage 4 | 4 | 1 (25%) | 3 (75%) | |
| 2 | Serum ferritin 500-1000 ng/ml | Stage 3 | 1 | 1 (100%) | 0 | 1.5 |
| | | Stage 4 | 1 | 0 | 1 (100%) | |
| 3 | Serum ferritin >1000 ng/ml | Stage 3 | 0 | 0 | 0 | 2.01 |
| | | Stage 4 | 2 | 0 | 2 (100%) | |

The children were grouped into mild, moderate and sever ferritin values [Mild elevation-Serum Ferritin less than 500 ng/ml, Moderate evelation-Serum ferritin 500-1000 ng/ml, severe ferritin elevation-Serum ferritin >1000 ng/ml]. The patients were grouped into 3 categories based on outcome values.

ed in other malignancies as well like neuroblastoma and breast carcinoma, in fact in neuroblastoma it acts as a guide for deciding therapy as a marker of disease activity [6-10]. HFE gene mutation has an association with childhood leukemia which has been showed by Dorak et al. [7]. In the study by Hann at 1990 with Hodgkin lymphoma of pediatric patients of all stages showed a level above 142 [8] microgram/l to have poor outcome. However in our study we included children only in stage 3 and 4 and the cutoff we found was higher with those reaching complete remission having a mean serum ferritin of 412 microgram/l compared to 728 microgram/l in those who had partial response. However the remission led to significant reduction of the ferritin level in both the groups with the group having complete remission reaching a mean serum ferritin level of 27.1 microgram/l compared to 495 microgram/l in those with partial remission and presence of disease activity. As there was no significant organ dysfunction noted statistically and transfusion burden was not significant the correlation between disease activity and ferritin level was established. The severity of presentation which was shown to increase above a value of 350 microgram/l as shown by Alvarez et al. [1] was close to our mean ferritin level of 412 microgram in responders to 6 cycles of ABVD.

Novelty of our study was the reduction in serum ferritn level with treatment indicating ferritin just like transferrin is possibly a marker of disease activity in pediatric Hodgkin disease and can act as a guide to determine the remission. Also the prognostic grouping of patients' needs to be done with ferritin values baseline values and the patients can be divided into 3 groups of prognosis based on these categories and outcome predictors. The response of ferritin with chemotherapy is also a stronger indicator for prognosis. Also unlike other lymphoreticular malignancies where iron overload due to blood transfusion is predominating cause of hyperferritinaemia, in Hodgkin disease the cause is more likely to be the disease process itself. Increasing ferritin level despite adequate treatment may be an indicator of treatment failure and work as predictor of mortality.

## Conclusion

From the findings in our study we can postulate that in Hodgkin disease serum ferritin level may be useful predictor of Hodgkin disease, activity and it can also act as an indicator of disease remission status.

## Disclosure of conflict of interest

None.

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