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Rate of Decline of Ferritin in Patients with Hemophagocytic Lymphohistiocytosis as a Prognostic Variable for Mortality

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is difficult to diagnose and treat. Highly elevated ferritin is strongly associated with HLH and levels may provide a prognostic marker. A comprehensive review of ferritin data from our patients during treatment was analyzed with respect to mortality. A patient was 17 times more likely to die when percent ferritin decrease was less than 50% as compared to a 96% or greater decrease as indicated with multivariate logistic modeling. Higher maximum ferritin levels in the first 3 weeks also contributed to the odds of death (OR=5.6;90%CI=1.2-24.9). Regular ferritin measurements may be useful predicting outcomes in HLH patients.

Keywords

Hemophagocytic Lymphohistiocytosis (HLH); ferritin; outcome; prognosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disease characterized by pathologic inflammation with abnormal cytokine production and is difficult to diagnose because clinical symptoms mimic many other diseases including viral, parasitic, or bacterial infections, autoimmune conditions, immunodeficiencies, and malignancy. [1,2,3] The pathophysiology of HLH involves infiltration of activated T-lymphocytes and macrophages into multiple organs. [4,5] Treatments involve both chemotherapeutic and immunomodulatory drugs with possible stem cell transplantation. Since diagnostic criteria and treatment regimens have been implemented, outcomes have significantly improved from a previous 95% mortality rate to a cure rate of 55%. [6,7] Early initiation of treatment is critical for enhancing the patients' chances of survival, therefore, improved diagnostic and prognostic indicators are needed.

Hyperferritinemia (>500 mg/L) is a diagnostic criterion for HLH and levels can be attained within a few hours. Ferritin is involved in regulation of iron storage and homeostasis. Ferritin is unlikely to contribute to pathology in HLH, but levels are a surrogate marker for inflammation because the gene promoter contains pro-inflammatory cytokine-responsive regulatory elements. We previously reported that ferritin values over 10,000 microgram/L are highly particularly helpful for the diagnosis of HLH. [8] In this report, we examine the usefulness of regular ferritin measurements for predicting outcome in patients with HLH.

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Methods

Ferritin levels, diagnostic criteria, and clinical outcome were obtained using medical chart review of 60 patients diagnosed and treated for HLH at Texas Children's Hospital (TCH) from 1991 through 2007. Approval to perform the study was given by Baylor College of Medicine Institutional Review Board. Ferritin measures were drawn throughout the diagnostic and treatment course at the discretion of the practitioners. Patients were excluded for having a single ferritin value (n=7) and/or >30 day gap between their maximum level and subsequent measurement (n=5).

Statistical Analysis

A percent change value of ferritin (FDD) was derived to summarize the ferritin trend. FDD was calculated as the amount of ferritin decrease from first ferritin measurement near diagnosis, and could be within a 2 week period prior to diagnosis, to minimal level reached during 0-10 weeks out from date of diagnosis, divided by the first ferritin measure, and multiplied by 100. The relative time variable, the number of days between first ferritin measure near diagnosis and minimum level, was adjusted for in the model.

The primary outcome was occurrence of death. The time to death/last follow-up variable was incorporated in the analysis, was shown to be an extraneous factor during the logistic regression modeling and subsequently eliminated from the model. Logistic regression was used to evaluate univariate relationships with the primary outcome. Variables found to be significant ($p<0.25$) by likelihood ratio chi-square test were considered for inclusion in the multivariate logistic regression model and included the following: age at HLH diagnosis, gender, season of year when HLH diagnosed, year of HLH diagnosis, maximum ferritin reached within first 3 weeks, days to maximum ferritin from first measurement, days from diagnosis to last follow-up or death, and days to diagnosis form first ferritin measurement. Presence or absence of fever, splenomegaly, liver enzyme levels, triglyceride levels, coagulation tests, and elements of the complete blood count were not significantly discriminating ($p>0.05$). There were insufficient data to test the strength of interleukin -2 levels, NK cell function, or presence or absence of genetic mutations associated with HLH to use in our model. Continuous variables were evaluated for linear scale in the logit. The G-test was used to assess interaction for all possible two-way product terms. Several of the product terms could not be tested for interaction due to sparse data within the strata. Both the Pearson chi-squared and the Hosmer-Lemeshow goodness-of-fit tests were computed for the final models. [9]

Results

Almost half (46%) of the 48 patients described in this study were diagnosed at less than 2 years of age. Average age was 4.5 years, ranging from 20 months to 16.6 years. The 16 males were younger (mean 3.6 years) than the 32 females (mean 5.0 years). The 580 ferritin values collected ranged from 1 to 180,760 mg/L through the course of treatment. Maximum ferritin values ranged from 333 to 152,573 mg/L within the first 3 weeks of treatment.

Univariate regressions identified age, gender, year of HLH diagnosis, and days to last follow-up or death for inclusion in the multivariate models. FDD contributed to the multivariate logistic regression model when fitted with these variables (Wald statistic $p<0.025$). Logistic regression procedures resulted in the exclusion of gender and days of follow-up. Maximum ferritin within the first 3 weeks was retained in the model as an explanatory variable, despite not showing significance during the univariate analysis. Of 24 patients with maximum ferritins of 11,000 μg/ml or less, 14 were alive and 10 died. Of those having a ferritin greater than 11,000 μg/ml, 11 were alive and 13 died. Multivariate

analysis resulted in a parsimonious model with the main effect of percent ferritin decrease (categorized ≤50%,51-92%,93-95%,≥96%), adjusted for time (categorized days ≤6, 7-30, 31-69), maximum ferritin level within first 3 weeks, year of diagnosis, and age (categorized years ≤1.5, 1.6-5.5, 5.6-16.6). In this model, patients with percent ferritin decrease less than 50% as compared to those with 96% or greater had an odds ratio for dieing of 17.42 (SE 24.97; 90% CI [1.65, 184.01]; p=0.046), controlling for variables in the model (Table I). Higher maximum ferritin levels in the first 3 weeks also contributed to the odds of death (OR=5.6;90%CI=1.2-24.9).

Discussion

In this analysis of ferritin levels in patients with HLH and outcome, a rapid rate of fall of ferritin levels following therapy initiation was associated with decreased mortality. This is clearly shown by statistical analysis of the data in Table I that proved that patients with less than a 50% drop in ferritin level as opposed to a 96% or greater drop had a 17-fold increased chance of dying. There are no standard outcomes predictors for HLH. It is often impossible to distinguish between familial HLH, which requires stem cell transplant, and acquired HLH, which may resolve with chemotherapy alone. Continuation therapy is needed for patients whose HLH has not completely resolved by the eighth week. HLH is prone to reactivation from triggers of the immune response including vaccination and new infections. [3] For those without a known family history or an identifiable genetic cause, changes in ferritin levels in response to the first eight weeks of therapy may aid the clinician in judging the responsiveness of the disease to medical treatment. [8] Relapsing disease may lead the clinician to further consider the need for transplant. Results from this study indicate that trends in ferritin levels are associated with mortality. A large prospectively designed study with regular ferritin, sCD25, and sCD163 measurements could further elucidate the predictive and descriptive value of these markers in HLH.

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Table I

HLH Mortality by Percent Ferritin Decrease

% Ferritin Decrease	Alive	Dead	Total
<=50%	4	8	12
51-92%	6	7	13
93-95%	6	4	10
>=96%	9	4	13
Total	25	23	48