

High Ferritin and Low Glycosylated Ferritin May Also Be a Marker of Excessive Macrophage Activation

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ABSTRACT. Objective. A high serum ferritin concentration with a low percentage of glycosylated ferritin (< 20%) have been reported to be a specific marker of active adult Still's disease (ASD). However, high ferritin levels are found during hemophagocytosis syndrome (HS). We investigated the ferritin level and the percentage of glycosylation in a HS series of various causes.

Methods. Diagnosis of HS was confirmed by erythrophagocytosis pictures on a bone marrow cytology or biopsy in all patients. Serum ferritin concentration was determined on a heterogenous immunoassay module. Glycosylated ferritin was separated using concanavalin A (Con-A) sepharose 4B chromatography. The nonglycosylated ferritin unbound to Con-A was recovered in the supernatant and quantified with the same procedure. Percentages of glycosylated ferritin less than 20% are considered to be usual in ASD, between 20 and 40% usual in inflammatory syndrome, and between 50 and 80% normal.

Results. In all cases tested during the acute phase of the disease, ferritin blood level was high and the percentage of glycosylated ferritin was low, less than 20%.

Conclusion. The combination of high ferritin level and low percentage of glycosylation may be a marker of excessive macrophage activation. (J Rheumatol 2003;30:1027–8)

Key Indexing Terms:

FERRITIN

MACROPHAGE ACTIVATION

GLYCOSYLATED FERRITIN
HEMOPHAGOCYTOSIS SYNDROME

Elevated serum ferritin concentration is a frequent finding in active adult Still's disease (ASD), and has been proposed as a criterion for the diagnosis of ASD¹. However, serum ferritin level is increased in inflammatory syndromes, and markedly elevated levels are found not only in ASD but also in hemophagocytosis syndrome (HS) and some liver cytolytic diseases². The differential diagnosis between active ASD and HS may be difficult. Although the hemogram is usually different in ASD and HS, with hyperleukocytosis and leukopenia, respectively, ASD and HS share some common symptoms — high fever, weight loss, hepatosplenomegaly, lymphadenopathy, rash, and liver dysfunction. Moreover, a confounding point is that hemophagocytosis has been reported during ASD^{3,4}. To improve the diagnostic specificity of ferritin level in active ASD, we investigated the value of ferritin isoforms and the percentage of glycosylation.

Two studies^{5,6} have shown that the combination of a high serum ferritin level and a low percentage of glycosylated ferritin (< 20%) was more specific of active ASD, as compared to other diagnostic markers and “may thus be especially helpful for the differential diagnosis of active ASD”⁵. Patients with ASD were compared with patients with systemic diseases, infections, and neoplasia. In the same study⁵, the mean ferritin glycosylation percentage in 120 patients with infectious, systemic, or liver diseases was 31.5% versus 15.9% ($p < 0.001$) in 49 patients with ASD. However, only 2 control cases had HS.

We investigated the ferritin level and the percentage of glycosylation in a series of cases of HS of various causes and evaluated the specificity of the combination of a high serum ferritin level and a low percentage of glycosylated ferritin.

MATERIALS AND METHODS

We reviewed all cases of HS diagnosed in our Internal Medicine Department during the last 3 years. The diagnosis of HS, suspected clinically, was confirmed by erythrophagocytosis pictures on a bone marrow cytology or biopsy in all patients. Serum ferritin concentration was determined on a heterogenous immunoassay module (Dimension RxL, Dade-Behring, Paris La Defense, France). Glycosylated ferritin was separated using concanavalin A (Con-A) sepharose 4B chromatography. The nonglycosylated ferritin unbound to Con-A was recovered in the supernatant and quantified with the same procedure. Percentages of glycosylated ferritin less than 20% are considered to be “usual in ASD,” between 20 and 40% “usual in inflammatory syndrome,” and between 50 and 80% normal⁷.

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RESULTS

Eight cases of HS were diagnosed since 1999. In one patient, ferritin level was unavailable. Causes of HS, ferritin levels, percentage of ferritin glycosylation, and the time of sampling (during acute disease or remission) are shown in Table 1. The underlying diseases were 6 cases of non-Hodgkin's malignant lymphomas (NHML) and 2 cases of severe drug hypersensitivity syndrome, an unusual cause of HS⁸. Ferritin blood level was high in all cases during the acute phase, mean $7545 \pm 7386 \mu\text{g/l}$ (95% CI 189) versus usual values in both male and female patients of 3 to 244 $\mu\text{g/l}$. Interestingly, as in ASD, the percentage of glycosylated ferritin was low, less than 20%, in all cases tested during the acute phase of the disease (mean $8.4 \pm 3\%$, 95% CI 0.08). During remission, while the ferritin level normalizes, the percentage of glycosylated ferritin remained low in 2/3 cases. This has also been reported in ASD remission⁹. This may suggest that in some patients with ASD or NHML, although they are considered to be in clinical remission, a low grade of macrophage activation persists. Contrasting with data reported in ASD, we did not find a correlation between C-reactive protein level and ferritin levels in the patients described.

DISCUSSION

We conclude the combination of high ferritin level and low glycosylation percentage is not specific to ASD, but is a marker of excessive macrophage activation. Inflammation and fever may induce a high ferritin level by the action of interleukin 1 β , which increases ferritin synthesis¹⁰. Liver

cell damage and ferritin release by macrophages after erythrophagocytosis may be other factors of high ferritin concentrations.

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Table 1. Characteristics of patients with hemophagocytosis admitted over 3 years.

Case	Sex/ Age	Diagnosis	Time of Sampling	Ferritin Level (normal < 300 $\mu\text{g/l}$)	GF, %	ESR, mm/h	CPR, mg/l	Fibrinogen, g/l	Leukocytes, /mm ³	Hb, g/dl	Platelets /mm ³	LDH (normal < 440 UI/l)	ASAT, (normal < 34 UI/l)	ALAT, (normal < 34 UI/l)	Bilirubin (normal < 17 $\mu\text{mol/l}$)
1	M 40	NHML	Acute disease	8283	7	11	67	1.2	1580	5.8	55,000	2694	154	408	177
2	F 52	Serious drug hypersensitivity syndrome	Acute disease	2470	ND	106	62	5.1	1800	7.3	17,000	1150	345	331	4
			At 6 mo	106	30	47	4	4.2	5520	11.1	180,000	N	N	N	N
3	F 35	NHML	Acute disease	746	7	125	16	1.1	1290	7.7	22,000	1405	95	44	10
4	F 23	NHML	Acute disease	1172	11	36	88	5.3	4400	9.2	348,000	1024	66	51	15
			Remission	120	5	4	6	3.8	4500	10.2	442,000	337	27	22	9
5	M 30	NHML	Acute disease	18,079	< 5	1	13	1.2	1490	9.3	82,000	5043	119	116	8
6	F 60	NHML	Remission	145	42	36	14	3.7	2330	12.3	212,000	N	N	N	N
7	F 45	Serious drug hypersensitivity syndrome	Acute disease	14,520	12	51	41	1.6	1200	8.1	100,000	3775	181	133	6

GF: glycosylated ferritin, N: 50–80%; NHML: non-Hodgkin's malignant lymphoma; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin; LDH: lactate dehydrogenase; ND: not done.