Acta Biomed 2018; Vol. 89, Supplement 3: 18-22 DOI: 10.23750/abm.v89i3-S.7213

Original article

The impact of iron overload in patients with acute leukemia and myelodysplastic syndrome on hepatic and endocrine functions

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Summary. Patients with hematologic malignancies undergoing chemotherapy and requiring blood transfusion usually have an elevated serum ferritin. These findings have led to the suggestion that iron overload is common and may have deleterious effects in these patients. However, the relationship between serum ferritin and parenchymal iron overload in such patients is unknown. Therefore, we measured the liver iron content (LIC) by the FerriScan® method and investigated the liver function and some endocrine tests in 27 patients with acute leukemia (AL) or myelodysplastic syndromes (MDS). Using FerriScan® method, the normal mean LIC levels are: 4.3±2.9 mg Fe/g dry weight (d.w.). In our patients, the mean serum ferritin level was 1965±2428 ng/mL. In our patients, the mean total iron in the blood received by them was 7177±5009 mg. In 6 out of 27 patients LIC was >7 mg Fe/g d.w. and in 11/27 serum ferritin was >1000 ng/ml. Measuring fasting blood glucose revealed 3/27 with diabetes mellitus and 4/27 with impaired fasting glucose (IFG). All patients had normal serum concentrations of calcium, parathormone (PTH), free thyroxine (FT4) and thyrotropin (TSH). Four patients had elevated serum alanine transferase (ALT). LIC was correlated significantly with ferritin level (r=0.5666; P<0.001) and the cumulative amount of iron in the transfused blood (r=0.523; P<0.001). LIC was correlated significantly with ALT (r=0.277; P = 0.04) and fasting blood glucose (FBG) was correlated significantly with the amount of iron transfused (r=0.52, p<0.01) and ALT level (r=0.44; P<0.01). The age of patients did not correlate with LIC, FBG or ALT. In conclusions, these results contribute to our understanding of the prevalence of dysglycemia and hepatic dysfunction in relation to parenchymal iron overload in patients with hematologic malignancies undergoing chemotherapy and requiring blood transfusions. (www.actabiomedica.it)

Key words: acute leukemia, myelodysplastic disorders, liver iron content (LIC), Ferriscan®, serum ferritin, alanine transferase

Introduction

Iron overload is common in patients with hematologic malignancies requiring repeated blood transfusions and may have a deleterious effect on the outcome of these patients. These findings have led to the suggestion that iron overload is common and may have deleterious effects in these patients. Nevertheless, we

have little understanding of the distribution of iron in these patients and its possible effects on hepatic and endocrine functions.

Although liver biopsy is the most accurate method to diagnose liver pathology and iron content of the liver it is inconvenient and has potential complications. This approach can be replaced using magnetic resonance imaging (MRI) techniques. A standardized and validated MRI method is now registered in Europe and the United States (FerriScan®), with reproducible relationship between the value (R2) obtained by MRI and liver iron content (LIC) assessed by biopsy This is potentially available in any hospital with an MRI scanner and with minimal training of local staff (1, 2).

We conducted this study in patients with myelodysplastic syndromes (MDS) or acute leukemia using hepatic FerriScan® method for the estimation of parenchymal iron overload prevalence and to clarify the relationship, if any, between iron burden, serum ferritin , liver enzymes and some endocrine functions.

Patients and methods

27 adult patients with acute myelogenous (AML) or lymphoblastic (ALL) leukemia (n=20) and MDS (n=7) were studied during their remission phase. We evaluated, in these groups of patients, using a cross-sectional study their serum ferritin levels, liver functions test, LIC and some endocrine functions. Both groups of patients were not receiving, before the study, iron chelation therapy. Lab. investigation, using standard commercial methods, included the measurement of fasting serum concentration of free thyroxine (FT4), thyrotropin (TSH), calcium, phosphate, parathormone (PTH, intact molecule). Fasting blood glucose and liver enzymes [serum aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP)] were also determined.

Liver iron content was measured using the Ferriscan® R2-MRI method (1-3).The method uses seven T2-weighted single spin-echo free-breathing sequences under fixed gain control with constant TR and increasing TE spaced at 1-3 ms intervals. The severity of liver iron overload was graded as following: LIC (severe) >15 mg Fe/g dry weight (d.w.), (moderate) 8-14.9 mg Fe/g d.w., and (mild) <8 mg Fe/g d.w. (1-3).

Definition of endocrinopathy categories

1. Evidence for diabetes mellitus: fasting glucose >6.9 mmol/l, and/or non-fasting glucose >11.1 mmol/l and/or exogenous insulin administration and/or use of oral hypoglycemic medications.

2. Evidence for primary hypothyroidism (low FT4, high TSH) or ongoing thyroid hormone replacement therapy.

Student “t test” was used to compare the laboratory data among the different groups when the data was normally distributed and Wilcoxon rank test when the data were not normally distributed. Linear regression equation was used to study possible correlations between different variables.

Institutional review board (IRB) approval was obtained from the HMC Research Center of Doha (Qatar) to perform the study.

Results

Lab investigations of 27 adult patients with acute and chronic leukemia who received chemotherapy and repeated blood transfusion showed that their mean serum ferritin was 1,965±2,428 ng/mL. Their mean total iron, received with blood transfusions, was 7,177±5,009 mg.

Diabetes mellitus, using the criteria of American Diabetes Association, was present in 3 out of 27 patients and impaired fasting glucose (IFG) in 4 out of 27 patients. All patients had normal serum concentrations of calcium, PTH, FT4 and TSH. Four patients had elevated ALT. LIC was correlated significantly with serum ferritin level ($r=0.567$, $P<0.001$) and the cumulative amount of iron received with blood transfusions ($r=0.523$, $p<0.001$). 11 out of 27 patients (40.7%) had a serum ferritin >1000 ng/ml. Using the FerriScan® method, the mean LIC was 4.3±2.9 mg Fe/g d.w. However, 6 out of 27 patients (22.2%) had a LIC >7 mg Fe/g d.w.

Comparison between acute and chronic cases showed that patients with acute leukemia had higher

serum ferritin concentrations and higher LIC compared to patients with chronic leukemia (Table 1).

LIC was correlated significantly with serum ferritin concentrations, ALT (r=0.277; P=0.04) and the amount of iron received with blood transfusions (Figure 1). FBG level was correlated significantly with the amount of iron transfused (r=0.52; P<0.01) and with ALT level (r=0.44; P<0.01). The age of patients did not correlate with LIC, FBG or ALT (Table 2).

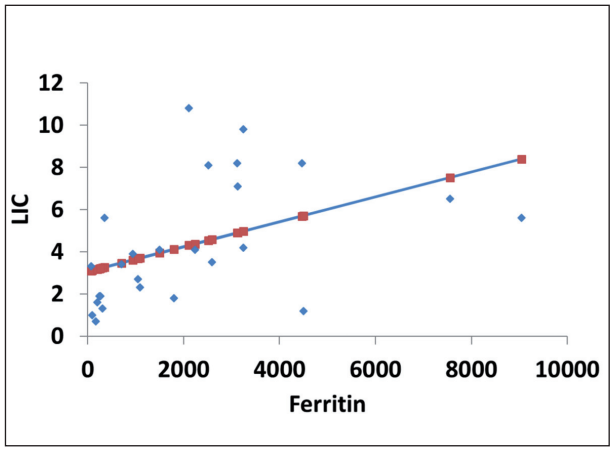

Figure 1. Correlation between serum ferritin and LIC (Ferriscan®) (r=0.566, P=0.0017)

Discussion

The accurate measurement of LIC is critical for the management of transfusional iron burden among patients receiving chronic transfusion therapy.

In this study, we report a high prevalence of hepatic iron overload, measured by FerriScan®, in patients with AML, ALL, or MDS. Although this is an indirect measurement, there was a strong correlation between liver T2* values and LIC measured by liver biopsy (1,3).

Our data also showed a higher prevalence of glucose homeostasis alterations and hepatic dysfunction in patients with acute and chronic malignancies requiring repeated blood transfusion.

Hepatic iron overload seems to be to be an important factor for both morbidities.

Table 1. Comparison between patients with acute versus chronic leukemia

	BMI	gender	Age	LIC	TSH	FT4	Ferritin	Transfused Fe	AST	ALT	ALP	Glucose (F)
Chronic Leukemias				ug Fe /g dry wt	uIU/ml	pmol/l	ng/ml	mg	U/L	U/L	U/L	mmol/L
Mean	29.54	5M	48.86#	3.00	1.56	13.28	1026.00	3066.00	19.71	26.00	90.14	6.20
SD	5.05	2F	14.68	2.97	0.64	1.46	1402.21	2154.00	7.91	21.25	33.84	1.52
Acute Leukemias												
Mean	24.70	18 M	32.43	4.38#	1.50	13.42	2731#	9352#	31.00	40.43	111.57	7.21
SD	4.41	2F	15.43	2.31	0.65	2.65	2200.00	4727.00	24.62	32.74	62.38	5.01

Abbreviations: aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP); #: p<0.05

Table 2. Regression analysis of different variables

	Age	LIC	TSH	FT4	Ferritin	Units bld	transfused iron mg	PTH	BMI	AST	ALT	ALP	Glucose (F)
Age	1.00												
LIC	-0.09	1.00											
TSH	0.11	-0.07	1.00										
FT4	0.03	0.25	-0.13	1.00									
Ferritin	-0.32	0.558#	-0.42	0.29	1.00								
Units bld	-0.10	0.47	-0.03	0.13	0.46	1.00							
transfused iron mg	-0.10	0.472#	-0.03	0.13	0.46	1.00	1.00						
PTH	-0.07	0.00	0.43	0.74	-0.29	-0.48	0.475#	1.00					
BMI	0.56	-0.28	0.27	0.42	-0.27	-0.30	-0.30	0.58	1.00				
AST	-0.17	0.01	-0.45	0.34	0.17	0.09	0.09	0.00	0.14	1.00			
ALT	-0.18	0.28	-0.36	0.20	0.21	0.12	0.12	-0.11	0.12	0.74	1.00		
ALP	-0.18	0.08	-0.17	0.30	0.71	0.08	0.08	0.26	0.10	0.03	0.00	1.00	
Glucose (F)	0.21	0.25	-0.10	0.15	0.21	0.52	0.52#	-0.31	0.14	0.36	0.45	0.04	1.00

Abbreviations: aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP); glusose (F): fasting; #: p<0.05

Although hepatic involvement in acute leukemia is usually mild and silent at the time of diagnosis, leukemic infiltration in both portal tracts and sinusoids occurs frequently, and massive leukemic cell infiltration of the liver may present as fulminant hepatic failure (4).

In addition, drug-induced liver injury, bacterial or fungal infections can negatively affect the liver functions. In our patients with leukemia, 4 out of 27 had elevated ALT levels associated with high serum ferritin and LIC. A positive correlation was found between the amount of iron received through blood transfusions, LIC and ALT levels. In brief, these data suggest a deleterious effect of hepatic iron overload on its function (5, 6).

Hepatic iron overload has been associated with glucose dysregulation (7, 8). This deleterious effect can be mediated through three key mechanisms: 1) insulin deficiency, 2) insulin resistance, and 3) hepatic dysfunction (9-11). In support of this concept, we found a significant correlation between LIC and FBG concentration and ALT levels in our patients with malignancy.

The role of iron in the pathogenesis of diabetes is suggested by the increased incidence of type 2 diabetes in diverse causes of iron overload (12-15) and by the reversal or improvement of glucose homeostasis after reduction of iron load achieved with phlebotomy or iron chelation therapy (15, 16).

One study suggested that an optimal threshold for starting iron chelation therapy in these patients is 2,500 ng/mL. This recommendation was based on the observed relationship between LIC and serum ferritin levels, that correspond roughly to an LIC value of 5 mg Fe /g d.w. However, a lower threshold of serum ferritin and a LIC may be adopted in these patients due to the presence other associated co-morbidities (17).

In our study, a comparison between patients with acute leukemia and chronic leukemia showed more hepatic iron overload and significantly higher ALT concentrations in the acute leukemia group. This can be explained by their greater transfusion requirement causing a significantly higher load of transfused iron.

Deferasirox is an oral iron chelator widely employed in the treatment of iron overload in thalassemic syndromes and recently has been shown to be effective in the treatment of patients with myeloproliferative disorders with iron overload. In chronically transfused MDS patients, deferasirox treatment produced a significant decrease in serum ferritin during 1 year of treatment. Improvements in ALT, which is an important indicator of hepatocellular injury, mirrored the reductions in serum ferritin and these changes were significantly correlated (18-20). Nevertheless, additional prospective studies are warranted to further investigate this association between iron burden and liver dysfunction in MDS.

In conclusion, patients with AL or MDS undergoing chemotherapy and repeated blood transfusions are at higher risk of increased parenchymal iron overload, hepatic dysfunction and dysglycemia. This can markedly increase their morbidity. It is suggested that oral chelation therapy based on evaluation of serum ferritin >1000 ng/ml or LIC >5 mg Fe/ g d.w. can significantly decrease these morbidities.

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Received: 12 March 2018
Accepted: 22 March 2018
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