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Potential effect of β thalassemia major on cardiac function among patients in Jeddah, Saudi Arabia

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Abstract

The present studydetect the prevalence of cardiac complications and the efficacy of iron overload monitoring by ECHO (LVEF), and serum ferritin assay in patients at Department of Clinical Hematology with β thalassemia major (βTM). Case records of all βTM patients were analyzed for clinical data, age, sex, heart failure, serum ferritin, ECG, chest x-ray and echocardiography. Sixty –two βTM patients with serially recorded LVEF are included in statistical analysis. Age range of these patients was 4-36 years. Clinical congestive cardiac failure (CHF) was observed in 5 patients(6.45%) with the age range of 13-28 years, 34 patients (54.8%) have normal ECHO findings while 28 patients (45.2%) have valvular heart disease, 8 patients (12.6%) had tricuspid regurgitation with pulmonary hypertension, and 20 patients (32.2%) had tricuspid, mitral or aortic regurgitation. The present study indicated that Observation of excess iron in the heart of βTM patients in King Abdulaziz University Hospital (KAUH) through LVEF and serum ferritin analysis have reduced incidence of CHF. LVEF instructs the use of intensive chelation therapy but cannot prevent or predict heart damage or CHF in the course of the disease; this may be due to the poor prognosis once CHF is occurred. More sensitive methods for early detection of cardiac complication arerequired as MRI T2* which is used to estimate myocardial iron and identifies pre-clinical cardiac iron deposition to prevent irreversible cardiac complication.

Introduction

Transfusions of blood and therapy with chelating iron has significantly increased the survival and decreased the morbidity in βTM. However, complications of heart remain constitute a significant morbidity and remain the reason of mortality in blood transfusion in patients with βTM [1]. 80% of patients had died by the age of 16 in the 1960's [2] and now at least80% survive beyond the age of 40 years but congestive cardiac failure (CHF), arrhythmias and premature deaths continue to occurred [3]. Some cases showed this was because of the difficulty in chelation treatment compliance, which was cumbersome [4], but also occurred even in some patients with well chelation therapy [5]. So, in all patients with βTM, regular evaluation of cardiac function is recommended [6] and is now an integral part of their management. However, the value of cardiac function monitoring by Echo Cardiology to the long-term management of βTM is unclear. This is partly because the prognostic significance abnormalities of diastolic pressure, which clear early in the disease process, are unknown [7]. Additionally, CHF is often already present by the time systolic abnormalities have become manifest using Echocardiography [8]. These manifestations have led some researcher to question the value of noninvasive monitoring of cardiac function in the thalassemia management [9]. Although recovery is possible in a proportion of patients with established CHF but long-term prognosis remains poor [10,11]. Monitoring of cardiac function should clearly identify patients athighest risk ofdecompensation of cardiac function before development of CHF.

Assessment myocardial iron and function by MRI has revolutionized the treatment of βTM patients and allows recognition of preclinical myocardial iron, stratifies prospective cardiac risk, and tracks response to modifications in iron chelation therapy [12]. This triggered us to evaluate the protocol applied in KAUH where the sequential quantification of ventricular function annually and in association with serum ferritin assay every 3 months is usedto identify early changes in the left ventricular ejection fraction (LVEF) from baseline for each patient which could be used for identifying patients at high risk and indicate the need for intensive chelation therapy.

In this study we estimated the frequency of cardiac complication and CHF in patients with β thalassemia major (βTM) in KAUH hospitalto evaluate the efficacy of regular monitoring of cardiac function and iron overload by echocardiography, LVEF, and serum ferritin.

Methods

This study included retrospective analysis of clinical records of 62 patients from140 patients with βTM followed up in the Clinical Hematology Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia between June 2003 and August 2010. We excluded 38 patients who do not have follow up results of Echo Cardiology. The result of Echo Cardiology, LVEF, and serum ferritin are available for 62 of 140 patients for whom the predictive value of LVEF monitoring is

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analyzed. Thirty seven patients were men and 25 women, and the mean age was 19.5 ± 7.3 years (range, 4-36 years). All patients underwent regular transfusions to maintain pre-transfusion hemoglobin levels higher than 9.5 g/dL.

Routine cardiac evaluation consisted of a detailed clinical history, physical examination, electro cardiography (ECG), and echocardiography. Impaired left ventricular (LV) function was defined as a decrease in resting LVEF either to a value below the lower reference limits of 45% or by more than 10% between 2 consecutive measurements, regardless of the LVEF value. Five patients had evidence of CHF during the period of observation (LVEF less than 45%) and later on died from CHF.

Chelation therapy was performed exclusively with deferoxamine mesylate (DFO), which consisted of a standard regimen (30-50 mg/kg per day by subcutaneous infusion 8-12h/d, 5-7 d/wk). DFO treatment was intensified in the event of objective evidence of asymptomatic LV dysfunction at rest to prevent progression to frank CHF or in case of CHF. Treatment was intensified using 24-hour continuous intravenous infusion of DFO (100 mg/kg) diluted in 500 to 1000 mL normal saline and delivered though a peripheral vein [13] for up to 1 week at a time to supplement ongoing subcutaneous treatment. Dosing intensification was reduced as serum ferritin values decreased in line with the therapeutic index, as previously describe [13].

Outcome measures and statistical analysis

The recorded variables were CHF and defined by the criteria of the Task Force on Heart Failure of the European Society of Cardiology [14]. To examine the relationship between serum ferritin concentration and cardiac risk, we divided the patients into 2 groups using the risk stratification criteria identified by Olivieri et al. [7] This analysis examines the effect of consistently high ferritin values (higher than 2500 g/L) on at least two occasions on survival. Summary data are presented as median or as mean ± SD. Pearson X^2 and Fisher exact tests were used to test the relationship between categorical variables. Differences between means of samples were analyzed using paired *t* tests. All statistical analyses were performed using SPSS software.

Results

Table 1 shows that cardiac complications have occurred in (53.2 %) of βTM patients but it caused only CHF and decreased LVEF less than 45% in (6.45%). Table 2 shows that the outcome was significantly higherin those patients who maintained serum ferritin values lower than 2500 g/L than patients their serum ferritin values higher than 2500 g/L (P = 0.05). The risk for death from iron overload was also significantly increased in this group (p = 0.001). Age and sex showed no effect on the incidence of CHF and mortality in thalassemia patients (P >0.05).

Table 1. Incidence of cardiac complication in β thalassemia patients.

B halassemia patients	62
Normal cardiac function	29 (54.8%)
Abnormal cardiac function	33 (53.2 %)
CHF	5 (6.45%)
Valvular Heart Disease	28(53.2%)
Tricuspid regurgitation with pulmonary hypertension	8(12.6%)
Tricuspid, mitral or aortic regurigation without pulmonary hypertension.	20 (24.1 %)
LVEF more than 45%	57 (91.9%)
LVEF lessthan 45%	5 (8.1%)

Table 2. Relationship between risk factors and cardiac complications.

Variables	No. of patients 62	CHF		Dead	Alive
		Yes	No		
Age	62	5 (8.1%)	57(91.9%)	4(6.5%)	58(93.5%)
Age(less than 15y.)	15(24.2%)	1(6.6 %)	14(93.3 %)	1(6.6%)	14(93.3%)
Age(more than 15y.)	47(75.8%)	4(8.5%)	43(91.5%)	3(6.4%)	44(93.6%)
Fisher exact test		0.62		0.86	
Sex (male)	37(59.7%)	3(8.1 %)	34(91.9%)	2(5.4 %)	35(94.6%)
Sex (female)	25(40.3%)	3(12 %)	22(88 %)	2(8%)	23(92%)
Fisher exact test		0.463		0.53	
LVEF <45%	5	5(100%)	0	4(20%)	1(80%)
LVEF ≥45%	57	0	57 (100%)	0	57 (100%)
Fisher exact test		0.001		0.001	
S.ferritin>2500 ug/l	43	5(11.6%)	38(88.4%)	4(9.3%)	39(90.7 %)
S.ferritin<2500 ug/l	18	0	19(100)%	0	18 (100)%
Fisher exact test		0.05		0.05	

Discussion

In our group of patients, LVEF performed with ECHO and serum ferritin was the regular tools for monitoring and adjusting therapy. This approach was not set up through a formal, prospective study; consequently, there is heterogeneity in patients' follow-up times and prior chelation histories. It is clear, however, that the incidence of HF is (6.45%) suggesting that this approach is useful. Our findings show that, using LVEF, a decrease in LVEF of more thanan absolute value below the reference rangeis associated with progression to clinical heart failure and death if DFO intensification is not achieved. In 4 patients it was not clear that detectable changes in systolic function by ECHO cardiography precede the development of clinical heart failure sufficiently early for a useful intervention strategy to be adopted. Inonepatient in the present study, LVEF changes were demonstrable before cardiac symptoms appeared.

Our findings may underestimate the effectiveness of the strategy used for LVEF monitoring and treatment intensification because in the older patients, baseline LVEF values were not obtained during childhood or early adolescence. Thus, a decrease in LVEF of 10% or more from the true baseline value could not be followed accurately, and intensification might have been delayed. However this protocol has given survival to some patients till the age of 34 years. These data reflect the effectiveness of DFO therapy when used in a centre in which monitoring and intervention are given high priority. However, the optimal age at which monitoring of ventricular function should best arted remains unclear. In the prechelation-era study by Engle *et al.* [2] the first signs of cardiac involvement emerged at approximately 10 years of age, with patients becoming symptomatic inmiddle to late adolescence. In our study, the 5 patient who had a LVEF of <45%, had initial normal LVEF and above 10 years. We suggest that yearly quantitative LVEF monitoring of patients hould begin ideally by 10 years of age.

In our study we found that the current protocol give decrease heart failure and this is contrary to Giardina *et al.* 1985 [13] who showed that monitoring of LV systolic function in thalassemia was traditionally considered of limited value because changes were only demonstrable as late events using echocardiography and is heavily dependenton operator skill [14]. This can be explained as the earliest echocardio graphic studies were conducted before current standard subcutaneous and intensive intravenous DFO regimens were available that used neither chelation nor sub therapeutic doses of DFO [13].

From this study we conclude that LVEF measurement associated with serum ferritin assay decreased incidence of CHF in patients with βTM in our hospital as it directs the use of intensive chelation therapy. However, LVEF by ECHO could not predict or prevent heart damage or CHF in the course of the disease; this may be due to the poor prognosis once CHF is occurred. Therefore, a new technique is recommended to be applied in our hospital as MRI which also used to estimate myocardial iron and identifies pre-clinical cardiac iron deposition [15,16].

So from this study we recommend the use of cardiac T2* in the treatment of βTM patients as it allows preclinical recognition of myocardial iron, stratifies prospective cardiac risk, and tracks response to modifications in iron chelation therapy. Use of cardiac T2* for the early identification and treatment of patients at risk is a legitimate means towards reducing the high burden of cardiac mortality.

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