

PREVALENCE AND RISK FACTORS FOR CARDIAC IRON OVERLOAD AND CARDIOVASCULAR COMPLICATIONS AMONG PATIENTS WITH THALASSEMIA IN NORTHERN THAILAND

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Abstract. Cardiovascular complications are the most common cause of death among thalassemia patients in Thailand. In this study, we evaluated the prevalence of cardiac iron overload, cardiovascular complications and the associated risk factors. The information obtained will serve as a guidance for surveillance, prevention and early treatment of the complications. We conducted a cross sectional study of Thai patients with thalassemia attending Chiang Mai University Hospital, Thailand. Cardiac T2* magnetic resonance imaging (CMR T2*) was used to evaluate the myocardial iron deposition and echocardiography was used to evaluate the cardiac function and to identify pulmonary hypertension. Ninety-one patients were included in the study; 64% females with a median age of 31 (16-75) years. Of the total study subjects, 49% had homozygous β thalassemia, 32% had β thalassemia/Hb E disease, and 19% had Hb H disease. Half the participants were transfusion-dependent and 84% had received iron chelation. The CMR T2* showed cardiac iron overload in 10 patients (11%). The maximum ferritin level in the previous 3 years was higher among the patients with cardiac iron overload (6,310 ng/ml) than among the patients without cardiac iron overload (3,352 ng/ml) ($p=0.001$). Twenty-one patients (23%) had cardiovascular complications. Cardiomyopathy was seen in 8% of patients [17% in patients with transfusion-dependent thalassemia (TDT) and none in patients with non-transfusion-dependent thalassemia (NTDT)] and pulmonary hypertension in 15% of patients (14% in patients with TDT and 16% in patients with NTDT). TDT and cardiac iron overload were significantly associated with cardiomyopathy. No risk factors were found to be significantly associated with pulmonary hypertension. In summary, cardiac iron overload and cardiomyopathy are important complications in TDT while pulmonary

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hypertension is seen in both TDT and NTDT. Iron chelation and monitoring of serum ferritin level will prevent cardiac iron overload and cardiomyopathy. Interval monitoring with echocardiography will help with early identification of the cardiac complications.

Keywords: cardiac complication, cardiac iron overload, pulmonary hypertension, thalassemia

INTRODUCTION

Cardiomyopathy and pulmonary hypertension are the most common causes of death among thalassemia patients (Olivieri *et al*, 1994; Borgna-Pignatti *et al*, 2005; Wood, 2009; Kremastinos *et al*, 2010). Different types of thalassemia predispose patients to certain cardiovascular complications (Aessopos *et al*, 2001; Aessopos and Farmakis, 2005; Aessopos *et al*, 2007). Cardiomyopathy is more common among transfusion-dependent thalassemia (TDT) patients while pulmonary hypertension occurs more commonly among non-transfusion-dependent thalassemia (NTDT) patients, especially in patients after splenectomy (Aessopos *et al*, 2001; Aessopos and Farmakis, 2005; Aessopos *et al*, 2007). Most studies have focused on cardiovascular complications occurring in beta-thalassemia patients (Olivieri *et al*, 1994; Phrommintikul *et al*, 2006; Charafeddine *et al*, 2008; Rutjanaprom *et al*, 2009; Anthi *et al*, 2013). Several studies have shown the efficacy of iron chelation in preventing and reversing serum and tissue iron of thalassemia patients (Farmaki *et al*, 2010; Danjou *et al*, 2013). This study aimed to evaluate the prevalence of cardiac iron overload and cardiovascular complications in patients with thalassemia in northern Thailand, and to identify risk factors for these conditions. The information obtained will serve as a guidance for surveillance, prevention and early treatment of the complications in patients with TDT and NTDT.

MATERIALS AND METHODS

We conducted a cross sectional study to evaluate the prevalence of cardiac iron overload and cardiovascular complications, and to identify risk factors for these complications in patients with thalassemia who attended the Adult Hematology Clinic at Chiang Mai University Hospital, Chiang Mai, Thailand from 1 June 2011 to 31 May 2012. The diagnosis of thalassemia in each subject was confirmed by a hematologist. Patients were classified as having TDT or NTDT. TDT was defined as requiring a red cell transfusion at least 3 times per year. Patients who were transfused fewer than 3 times per year were classified as having NTDT.

Patients were evaluated for cardiac complications with a questionnaire and physical examination. Cardiac T2* magnetic resonance imaging (CMR T2*) was used to evaluate myocardial iron deposition and echocardiography was used to evaluate cardiac function and to identify pulmonary hypertension.

Echocardiography

Echocardiography was conducted by a cardiologist and included two-dimensional, M mode, and Doppler (pulsed wave, continuous wave and color) echocardiography performed at rest. Left ventricle dimensions were measured and classified following the American Society of Echocardiography recommendations (Phrommintikul *et al*, 2006). The modified Simpson's Rule was used to measure left

ventricular ejection fraction (LVEF). Pulmonary artery pressure was estimated by measuring the systolic transtricuspid pressure gradient from tricuspid regurgitation and adding it to the right atrial pressure, which was estimated by the response of the inferior vena cava to inspiration. Cardiac complications were defined as: functional impairment of ventricular filling (LVEF <55%) or pulmonary artery hypertension diagnosed by a pulmonary arterial pressure (PAP) of >35 mmHg.

Cardiac magnetic resonance imaging

CMR T2* imaging was performed with a 1.5-Tesla (T) Achieva Philips magnetic resonance imaging scanner, (Best, The Netherlands) as described previously (Inthawong *et al*, 2015), using a SENSE cardiac phase array equipped with a 5 channels coil. The black blood Gradient Echo multi-echo pulse sequence was used for this study. The scanning protocol was slightly modified from that of standard protocols (Anderson *et al*, 2001; Wood *et al*, 2004) with the first TE = 1.7 milliseconds (ms) at an increment of 2.7 ms, a matrix size of 156 x 112, a field of view (FOV) of 36 cm x 36 cm, a slice thickness of 10 mm and a TR of 28 ms. Images of the mid short axis inter-ventricular septum were acquired at 10 Echo times. The acquired images were fitted for the T2*s using a simple mono-exponential (SME) model or offset model (mono-exponential plus a constant). For severe iron overload cases, late echo truncation with the SME model or offset model was usually necessary for T2* curve fitting.

Demographic data collected from subjects included age, sex, type of thalassemia, history of underlying disease, history of blood transfusions, history of iron chelation and history of splenectomy. These data were obtained from the medi-

cal record along with the results of previous laboratory tests.

A complete blood count (CBC), liver function test (LFT) and serum ferritin level were obtained from each subject at the time of enrollment. Serum ferritin levels for the 3 years prior to enrollment were also obtained from the medical record. The maximum ferritin level in the previous 3 years was recorded and the mean ferritin level was calculated for each subject.

Data analysis

Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL). Descriptive data were reported as percentages, means, minimums, maximums and standard deviations. Logistic regression analysis was used to analyze relationships between cardiac iron overload, cardiovascular complications and risk factors. A *p*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Ninety-one patients were included in the study. The patient characteristics are summarized in Table 1. Homozygous beta thalassemia (45 patients, 49%) and beta thalassemia/Hb E disease (29 patients, 32%) were the most common types of thalassemia present among study subjects. Seventeen patients (19%) had Hb H disease or Hb H/Hb Constant Spring disease (alpha-thalassemia).

Iron chelation treatment

Seventy-six patients (84%) had received iron chelation (Table 1). Deferiprone is the most frequently used iron chelator at our center. Despite iron chelation therapy, 63 patients (69%) had a mean serum ferritin level >1,000 ng/ml and 16

Table 1
Clinical and laboratory characteristics of the patients (N=91).

Patient characteristics	No. (%)
Gender	
Male	33 (36)
Female	58 (64)
Mean age (years)	34 ± 14.6
Thalassemia type	
Homozygous beta thalassemia	45 (49)
Beta thalassemia/Hb E disease	29 (32)
Hb H disease and Hb H/Constant Spring disease	17 (19)
Transfusion dependency	
Transfusion-dependent thalassemia	42 (46)
Non-transfusion-dependent thalassemia	49 (54)
History of splenectomy	58 (64)
Iron chelation	76 (84)
Desferrioxamine	13 (17)
Deferiprone	38 (50)
Combined desferrioxamine and deferiprone	10 (13)
Deferasirox	15 (20)
Mean pre-transfusion hemoglobin level (g/dl)	7.1 ± 1.3
Mean ferritin level	
Maximum 3-year ferritin level (ng/ml)	3,821 ± 2,106
Ferritin level at enrollment (ng/ml)	1,784 ± 1,347

patients (17.6%) had a mean serum ferritin level >2,500 ng/ml.

Cardiac iron overload

The CMR T2* with a shorter signal of < 20 ms, suggesting cardiac iron overload, was found in 10 patients (11%). The maximum ferritin level during the previous 3 years was higher among subjects with cardiac iron overload (6,310 ng/ml) than among subjects without cardiac iron overload (3,352 ng/ml) ($p=0.001$).

Cardiovascular complications and risk factors

Twenty-one patients (23%) had cardiovascular complications. Seven patients (8%) had cardiomyopathy and 14 patients (15%) had pulmonary hypertension. The

clinical and laboratory characteristics of the groups with and without cardiomyopathy are shown in Table 2. All patients who had cardiomyopathy had TDT. The prevalence of cardiomyopathy among subjects with TDT was 17%. The factors associated with cardiomyopathy were TDT and cardiac iron overload. Age, sex, volume of red cell transfusion per year, history of splenectomy, hemoglobin level, platelet count, and ferritin level were not significantly associated with the presence of cardiomyopathy.

Among patients with pulmonary hypertension, 8 (9%) had NTDT and 6 patients (6%) had TDT. None of the factors, including the age, sex, diagnosis of TDT, volume of red cell transfusion per

Table 2
Clinical and laboratory characteristics of the thalassemia patients with and without cardiomyopathy.

Clinical and laboratory characteristics	Patients with cardiomyopathy (N=7)	Patients without cardiomyopathy (N=84)	p-value
Age (years)	22.3 ± 3.0	30.9 ± 1.9	0.26
Gender: Female	6 (85.7%)	52 (61.9%)	0.21
Diagnosis of TDT	7 (100%)	35 (41.7%)	0.002
Volume of red cell transfusion (unit/year)	20.6 ± 5.9	10.9 ± 7.3	0.34
History of splenectomy	4 (57.1%)	54 (64.3%)	0.61
Hb level (g/dl)	7.2 ± 0.6	6.8 ± 1.1	0.32
Platelet count (/mm ³)	901,570 ± 278,810	633,040 ± 287,650	0.77
Maximum 3-year ferritin level (ng/ml)	2,758 ± 1,312	2,079 ± 1,697	0.83
Cardiac T2* <20 ms	7 (100%)	4 (4.8%)	<0.001

Table 3
Clinical and laboratory characteristics of the thalassemia patients with and without pulmonary hypertension.

Clinical and laboratory characteristics	Patients with pulmonary hypertension (N=14)	Patients without pulmonary hypertension (N=77)	p-value
Age (years)	32.9 ± 15.8	28.9 ± 11.7	0.09
Gender: Female	9 (64.3%)	49 (63.6%)	0.96
Diagnosis of TDT	6 (42.9%)	36 (46.8%)	0.79
Volume of red cell transfusion (unit/year)	7.1 ± 3.6	13.3 ± 8.1	0.79
History of splenectomy	9 (64.3%)	49 (63.6%)	0.89
Hb level (g/dl)	6.9 ± 0.9	6.8 ± 1.1	0.26
Platelet count (/mm ³)	582,000 ± 256,680	691,910 ± 307,000	0.22
Maximum 3-year ferritin level (ng/ml)	2,037 ± 1,239	2,212 ± 1,726	0.84
Cardiac T2* <20 ms	1 (7.1%)	9 (11.7%)	>0.99

year, history of splenectomy, hemoglobin level, platelet count, ferritin level and cardiac iron overload, were associated with pulmonary hypertension (Table 3).

DISCUSSION

Cardiomyopathy is an important complication and major cause of death

among patients with thalassemia (Olivieri *et al*, 1994). The prevalence of cardiomyopathy (EF<55% on echocardiogram) in our study was 8% for all patients and 17% for patients with TDT, lower than a report in 1987 which reported prevalence of cardiomyopathy of 58% among thalassemia patients in Thailand who had not received iron chelation therapy (Sudhas

Na Ayuthya *et al*, 1987). These differences probably reflect the effects of iron chelation therapy in our study population reducing the risk for iron overload and cardiomyopathy. The lower prevalence of cardiomyopathy in our study is in agreement with Olivieri *et al* (1994) who found that iron chelation reduced the prevalence of cardiomyopathy and improved survival. In the early days of iron chelation therapy when only desferrioxamine was available, cardiomyopathy prevalence worldwide was approximately 37% (Olivieri *et al*, 1994). As a result of advances in iron chelation therapy, the global prevalence of cardiomyopathy has decreased to 8-15%, comparable to our current study (Li *et al*, 2002; Aessopos and Farmakis, 2005; Borgna-Pignatti *et al*, 2005).

At our center, iron chelation is given to patients with serum ferritin levels greater than 1,000 ng/ml. In the past, desferrioxamine was the only agent available. Nowadays, 3 iron chelating agents are available: desferrioxamine, deferiprone and deferasirox. However, the accessibility to these agents, especially deferasirox, is limited due to high cost (Viprakasit *et al*, 2009; Rachmilewitz and Giardina, 2011). Deferiprone is the most common agent used at our institution. Although most patients (84%) in our study had received iron chelation treatment, more than half had ferritin levels >1,000 ng/ml and 16 patients had ferritin levels >2,500 ng/ml, placing them at high risk of developing cardiac iron overload and cardiac complications (Olivieri *et al*, 1994; Borgna-Pignatti *et al*, 2004). Our study confirms the finding that patients with high ferritin levels are at high risk for cardiac iron overload as measured by CMR T2*.

A CMR T2* <20 ms, reflecting a high myocardial iron level has been reported to be associated with decreased LV func-

tion (Anderson *et al*, 2001; Carpenter *et al*, 2013). CMR T2* has been reported to detect cardiac iron overload prior to clinical cardiomyopathy (Pennell, 2005; Koonrungsomboon *et al*, 2013). All 7 patients in this study who had cardiomyopathy had myocardial iron overload identified by CMR T2*, and none with a normal CMR T2* result had impaired cardiac function.

Several factors have been reported to be associated with pulmonary hypertension among thalassemia patients, such as splenectomy, high platelet counts, increased nucleated red blood cells, NTDT and history of thrombosis (Phrommintikul *et al*, 2006; Karimi *et al*, 2011; Atichartakarn *et al*, 2014). In our study, 15% of patients had pulmonary hypertension but no factors were found to be associated with pulmonary hypertension. There was a higher prevalence of pulmonary hypertension among splenectomized patients in our study but the difference was not statistically significant. The 15% prevalence of pulmonary hypertension in our study was low compared to some studies of 40-60% (Aessopos and Farmakis 2005; Phrommintikul *et al*, 2006; Atichartakarn *et al*, 2014). The heterogeneity of our study population, comprised of both TDT and NTDT patients, alpha and beta thalassemia, may have contributed to this negative finding for identifying factors associated with pulmonary hypertension. The number of splenectomized patients in our study was high (64%) suggesting a unique population compared to other studies (Aessopos and Farmakis 2005; Phrommintikul *et al*, 2006; Atichartakarn *et al*, 2014).

A limitation of our study was the small sample size, especially among alpha thalassemia patients ($n=17$). The heterogeneous composition of study subjects and inclusion of both those with TDT

and NTDT make associations difficult to determine.

In summary, the prevalence of cardiac iron overload and cardiovascular complications in patients with thalassemia are high. Cardiac iron overload was seen in 11% of the patients. Cardiomyopathy was seen in 8% of patients (17% in patients with TDT and none in patients with NTDT). Pulmonary hypertension was seen in 15% of patients (14% in patients with TDT and 16% in patients with NTDT). TDT and cardiac iron overload were significantly associated with cardiomyopathy. However, we were unable to find any factors significantly associated with pulmonary hypertension. Iron chelation and careful monitoring of serum ferritin level will prevent the cardiac iron overload and cardiomyopathy in patients with TDT. Interval monitoring of patients with TDT or NTDT with echocardiography will help with early detection of cardiomyopathy and pulmonary hypertension.

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