Early Detection of Cardiac Involvement in Beta-Thalassemia Children

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Abstract

Background : Beta-thalassemia major and beta-thalassemia/HbE are the important causes of chronic hemolytic anemia in Thailand. The objectives of the study were to determine variables associated with cardiac involvement in asymptomatic beta-thalassemia patients.

Patients and Method : The authors studied beta-thalassemia major and beta-thalassemia/HbE patients who came to the clinic between July 1st 1999 and July 31st 2000. There were 211 asymptomatic patients included in study. Their ages ranged from 2.6 to 18.2 years. Previous clinical history including blood transfusion and iron chelation were recorded. All patients received a thorough physical examination, chest X-ray, electrocardiogram and echocardiogram. Patients who had abnormal systolic or diastolic function detected by echocardiogram were identified as having cardiac involvement.

Results : Cardiac involvement was found in 26 patients (12.3%). There was no difference in physical examination between patients who had and did not have cardiac involvement. Abnormal chest X-Ray defined as cardiothoracic (CT) ratio>0.55 and electrocardiogram (ECG) findings of left or right ventricular hypertrophy were associated with cardiac involvement. Other associated findings were older age and lower average pretransfusion hematocrit ($23 \pm 6.6\%$).

Conclusions : In asymptomatic beta-thalassemia children, chest X-ray and ECG should be used for screening patients for the detection of cardiac involvement.

Key word : Beta-Thalassemia, Cardiac Involvement, Children, Thailand

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Beta-thalassemia major and beta-thalassemia/hemoglobin (HbE) are the important causes of childhood chronic hemolytic anemia in Southeast Asia[1-4]. Cardiac involvement is the cause of death in almost 60 per cent of thalassemia major patients [5-7]. Severe beta-thalassemia/HbE patients may also have clinical features of beta-thalassemia major. Cardiac involvement in beta-thalassemia major patients reported as early as 1964[8]. However, little is known about the cardiac involvement in patients with beta-thalassemia in children[9-12]. A previous study in Thailand revealed an iron deposition in 32 per cent of cardiac tissue in autopsied patients who had beta-thalassemia/HbE disease[9]. A report from adult thalassemia patients in Thailand revealed that 11.9 per cent had cardiac involvement[2]. The objectives of this study were to identify asymptomatic beta-thalassemia children who had cardiac involvement.

PATIENTS AND METHOD

Patients

Homozygous beta-thalassemia and beta-thalassemia/HbE patients attending the hematology clinic between July 1st 1999 and July 31st 2000 who had been followed-up for at least two years were included in the study. Their ages were from 2 to 18 years. The study was approved by the ethical committee of Siriraj Hospital. The patients were divided into two groups: Group I were patients without cardiac involvement and Group II were patients with cardiac involvement. The demographic data and treatment history including blood transfusion were retrospectively reviewed in each patient from the medical records. The dosage of the blood transfusion was calculated as each transfusion consisted of 10 ml/kg leukocyte poor packed red cells. Average pretransfusion hematocrit level, serum ferritin level and chelation dosage (mg/of desferrioxamine/week) were recorded. Each patient was evaluated by thorough physical examination by the primary investigators (VT, SK). The details of the physical examination focusing on the evidence of heart failure such as cardiomegaly, heart murmur, and pulmonary or systemic venous congestion were recorded. Each patient had bedside investigations including a pretransfusion hematocrit, serum ferritin, chest radiograph (CXR) and electrocardiogram (ECG). An echocardiogram (ECHO) was performed in each patient in order to evaluate any structural defect or degree of cardiac enlargement at the same visit. Systolic or diastolic dysfunction was also evaluated in each patient. The cardiac index (cardiac output/body surface area) was also measured[13]. The results of the CXR, ECG and ECHO were independently interpreted by the primary investigators (KD, SK).

Cardiac complications were defined as an echocardiographic examination result showing systolic dysfunction (decreased ejection fraction <40%) or diastolic dysfunction (such as abnormal relaxation pattern or restrictive physiology on mitral inflow Doppler)[14].

Statistical analysis

All measured variables were expressed as mean±SD, whereas, categorical variables were presented as frequency count and percentages. The patients were divided into two groups; patients with cardiac involvement and patients without cardiac involvement. Differences between the two groups were assessed by using the student *t*-test or chi-square test where appropriate. The results were considered to have statistical significance when the p-value was less than 0.05. All tests and p-values were calculated as two-tailed values.

RESULTS

There was a total of 215 patients, enrolled in the study. This group of patients represented the majority of thalassemia major and beta-thalassemia/HbE patients who are currently being followed-up by the authors. 211 patients did not have any signs of congestive heart failure during the study period, while 4 patients were admitted and treated specifically for congestive heart failure. Of these 211 asymptomatic cases, 102 (48.3%) were males and, 109 (51.7%) were females. Their ages ranged from 2.6-18.2 years, with a mean age of 8.9 ± 3.8 years. There were 130 patients (61.6%) who received hypertransfusion and iron chelation. Beta-thalassemia major and B-thalassemia/HbE accounted for 54 patients (25.6%) and 157 patients (74.4%) respectively. There were 26 patients (12.3%) who had cardiac complications ranging from cardiomegaly (more than 2 SD), poor systolic function with ejection fraction (EF) <40 per cent or diastolic dysfunction.

Physical examination revealed that 47 patients had cardiac murmur, and 22 patients had cardiomegaly. Only 7 patients had signs of cardiac failure, one patient with pulmonary venous conges-

tion and six patients with systemic venous congestion. Only one patient had respiratory distress on routine examination.

Comparison of patients who had and did not have cardiac involvement (Table 1 and 2)

There were 26 patients (12.3%) with cardiac involvement (Group II). The comparison between each variable is shown in Table 1 and 2. Patients who had cardiac involvement were older (11.4 ± 4.5 years old) when compared with normal patients (Group I) who did not have cardiac complications (8.6 ± 3.6 years old, p=0.001). Positive physical findings such as cardiac murmur, cardiomegaly, sign of pulmonary venous congestion and systemic venous congestion were not different in both groups. An electrocardiogram was performed on 195 patients. Right ventricular hypertrophy (RVH) and left ventricular hypertrophy (LVH) were found in 26.9 per cent and 73.1 per cent of the patients in Group II which were significantly higher than those found in the children in Group I who had RVH and LVH at 9.7 per cent and 28.6 per cent respectively.

There were 182 patients who had CXR. Twenty five patients (11.6%) had cardiomegaly (defined as cardiothoracic ratio (CT) >0.55). About one third of the Group II patients (34.6%) had cardiomegaly on CXR when compared with 9.9 per cent

Table 1. Physical signs, laboratory assessments of cardiac function and treatment history of beta-thalassemic patients with and without cardiac involvement.

	No cardiac involvement n=185	Cardiac involvement n=26	P-value
Age (yr)	8.6 ± 3.6	11.4 ± 4.5	0.001*
Weight (kg)	23.7 ± 9.8	25.1 ± 9.6	0.440
Height (cm)	120.5 ± 17.2	125.5 ± 18.4	0.174
O_2sat (%)	98.6 ± 9.5	98.5 ± 9.4	0.854
Avr-Hct (%)	27.5 ± 4.5	23 ± 6.6	0.001*
SBP (mmHg)	98.7 ± 9.5	98.5 ± 9.4	0.955
DBP (mmHg)	52.0 ± 9.2	51.9 ± 8.6	0.950
Txonset (age-yr)	3.1 ± 3.1	4.2 ± 2.5	0.101
Avr-Tx (dose/kg/yr)	11.3 ± 7.6	8.7 ± 9.0	0.121
DFO (mg/wk)	3,750 ± 1,909	4,583 ± 2,872	0.416
Duration chelation (months)	53.2 ± 45.8	74.6 ± 45.9	0.210
Ferritin (ng/ml)	3,490 ± 2,963	2,579 ± 2,892	0.158
CT ratio	0.50 ± 0.04	0.53 ± 0.06	0.034*
EF (%)	62.3 ± 6.5	45.6 ± 3.2	0.001*
CO (l/min)	4.0 ± 1.6	5.6 ± 1.4	0.001*
CI (l/min/m^2)	4.7 ± 1.4	6.9 ± 1.6	0.001*
RVSP (mmHg)	29.7 ± 8	33.4 ± 9.4	0.031*
E vel (m/sec)	1.3 ± 1.3	1 ± 0.22	0.301
Avel (m/sec)	1.0 ± 0.5	0.54 ± 0.17	0.609
E:A	2.1 ± 2.1	2.0 ± 0.8	0.705
Mitral DT (msec)	115 ± 27	135 ± 42	0.003*
PulS (m/sec)	0.61 ± 0.2	0.61 ± 0.1	0.986
PulD (m/sec)	0.56 ± 0.1	0.53 ± 0.1	0.452
Atr (m/sec)	0.31 ± 0.1	1.17 ± 0.9	0.006*

* p = <0.05

O_2 sat = Oxygen saturation, Avr-Hct = Average level of pretransfusion hematocrit over follow-up period, SBP = systolic blood pressure, DBP = diastolic blood pressure, Txonset = age at first blood transfusion, Avr-Tx = blood transfusion (unit as D/yr = dose per year), DFO = desferrioxamine, CT ratio = Cardiothoracic ratio from chest X-ray, EF = Ejection fraction (%), CO = cardiac output (l/min), CI = cardiac index (l/min/m^2), RVSP = Right ventricular systolic pressure (mmHg), E vel = E wave velocity (m/sec) from mitral inflow Doppler, A vel = A wave velocity (m/sec) from mitral inflow Doppler, E:A = ratio of E wave to A wave, Mitral DT = mitral deceleration time (msec), Pul S = pulmonary vein inflow velocity (m/sec) during systole, Pul D = pulmonary vein inflow velocity (m/sec) during diastole, Atr = atrial reversal velocity (m/sec).

Table 2. Variables associated with cardiac involvement.

Variables	Normal n=185		Cardiac involvement n=26		P-value
		%		%	
Male	87	47	15	57.7	0.308
Beta-thalassemia major	50	27.2	4	15.4	0.198
CT ratio>0.55	16	9.9	9	34.6	0.001*
RV enlargement by ECG	18	9.7	7	26.9	0.014*
LV enlargement by ECG	53	28.6	19	73.1	0.001*
ST-T change by ECG	7	4	3	15	0.035*
Cardiac enlargement by ECHO	40	21.6	9	34.4	0.032*
Pericardial effusion	1	1.9	5	19.2	0.598
mitral regurgitation	5	9.1	14	53.3	0.959
Hypertransfusion	121	65.4	9	34.6	0.003*
Chelation	102	55.1	9	34.6	0.05*
Splenectomy	36	19.5	9	34.6	0.077
PHT (RVSP>30 mmHg)	51	32.3	14	60.9	0.008*

* p = 0.001

CT ratio = Cardiothoracic ratio by chest X-ray,
PHT = pulmonary hypertension measured by echocardiogram with right ventricular systolic pressure (RVSP).

in Group I patients ($p<0.005$) as shown in Table 2. Average pretransfusion hematocrits (Hct-avr) were calculated from hematocrits taken over the follow-up period. It was found that patients who had cardiac involvement had significantly lower average pre-transfusion hematocrits (23 ± 6.6%) when compared with the normal cardiac function group (27.5 ± 4.5%, p=0.001).

Echocardiographic findings

Cardiomegaly was found in 34.6 per cent of the patients in Group II who had cardiac involvement. Abnormal systolic function (poor contractility) was found in 14 patients (average ejection fraction of 45.6 ± 3.2% compared to 62.3 ± 6.5% in the normal group, p=0.001), Table 1. Pericardial effusion was found in 5 patients (19.2%). Mitral regurgitation was found in 14 patients (53.3%) with cardiac involvement.

Only 34.6 per cent of the patients in Group II were hypertransfused which is significantly lower than 64.5 per cent the patients in Group I who had no cardiac involvement (p=0.003). However, there were no differences in serum ferritin values and the dosage of iron chelation between both groups.

DISCUSSION

Beta-thalassemia is an inherited hemoglobin disorder caused by impaired synthesis of the β-globin chain resulting in chronic hemolytic anemia. Cardiac involvements is the main feature of clinical spectrum of beta-thalassemia, and is the leading cause of death which has been well documented[3-5] in thalassemia. The prominent finding in this condition is left ventricular (LV) dysfunction, which is attributed mainly to iron overload and leads gradually to cardiac failure and cardiogenic death[15,16]. However, valvular involvement and pericardial thickening or effusion has also been reported[17].

A few studies[6,10-12] have noticed this involvement in children and young adults with thalassemia. The authors conducted a cross sectional study to evaluate the frequency of cardiac complications of patients aged from 2 to 18 years who had thalassemia and who had been followed-up for at least two years. The gold standard criteria for cardiac involvment were defined as severe systolic or diastolic dysfunction that was diagnosed on echocardiogram. The authors then tried to find independent variables (e.g. demographic data, history of blood transfusions, physical examination, and routine laboratory investigations) that were associated with cardiac complications in this group of patients.

Older age and longer follow-up period were found to be associated with a higher chance of having cardiac complications. The type of thalassemia and percentage of each type of abnormal hemoglobin at first diagnosis were not associated

with cardiac complications. Physical findings such as cardiac murmur detected by the primary investigator (VT, SK) were not clinically useful, since a cardiac murmur from high cardiac output state is often heard in children with thalassemia who have a hemoglobin level of less than 8 g/dl[11] as demonstrated in 47 patients (21.6%) in the present study. Associated symptoms of exertional dyspnea and easy fatigability were frequent in anemic patients. Sign of congestive cardiac failure may be somewhat difficult to detect in patients with a normal functional class. Enlargement of cardiac chambers, in particular, the left ventricular hypertrophy was found significantly higher in the group of patients with cardiac involvements. Increased CT ratio (>0.55) was found in 9 out of 26 patients (47.4%) with cardiac complication.

When the authors reviewed the history of blood transfusion in each patient, it appeared that patients who had cardiac complications had a slightly lower average hematocrit (Hct were obtained before transfusion at each visit and the value was averaged over the follow-up time) which was 23 ± 6.6 per cent when compared with 27.5 ± 4.5 per cent of normal cardiac function group (p=0.001). As expected in the group of patients who had hypertransfusion, there were fewer patients with cardiac involvement. Chronic anemia can affect the long-term high output condition which can eventually cause cardiomegaly or myocardial dysfunction.

Echocardiographic study

In the present study patients with severe systolic dysfunction (low ejection fraction with or without cardiac enlargement) and diastolic dysfunction (restrictive physiology) on echocardiographic examination were classified as having cardiac involvement. As a result, it was also found that patients with cardiac involvement had a higher cardiac index than patients in the normal cardiac function group (Table 1). It was also found that patients with cardiac involvement had a slightly higher right ventricular systolic pressure (RVSP) of 33.4 ± 9.4 mmHg when compared with the normal cardiac function group (29.7 ± 8 mmHg, p=0.03). The frequency of cardiac involvement in beta-thalassemia major or beta-thalassemia/HbE patients was comparable with previous studies[2,17]. A few patients were also noted to have diastolic dysfunction as in previous studies[17-19].

Echocardiogram is a non-invasive tool to evaluate cardiac dysfunction. However, it is not always readily available for the evaluation of individual patients. Also, the interpretation of the echocardiogram is operator dependent. They objective of the present study was to try to identify any clinical or laboratory factors that could help in early detection of patients with cardiac involvement. It was found that in asymptomatic beta-thalassemia patients, chest radiographs showing cardiomegaly (CT ratio>0.55) with chamber enlargement by ECG findings could be used to screen cardiac involvement. These patients should be sent for further echocardiographic examination for early detection of cardiac complications.

SUMMARY

The study objective was to try to identify any clinical or laboratory factors that could help in the early detection of patients with cardiac involvement. The authors found that factors associated with cardiac complications in pediatric patients who had beta-thalassemia were: older age, longer follow-up period, lower average pretransfusion hematocrit (23%), cardiomegaly on chest radiograph (CT>0.55), and abnormal ECG findings.

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การวินิจฉัยภาวะผิดปกติทางหัวใจในผู้ป่วยเด็กที่เป็นเบต้าธาลัสซีเมีย

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ที่มา : ผู้ป่วยเด็กที่เป็นเบต้าธาลัสซีเมียเป็นสาเหตุสำคัญที่ทำให้มีภาวะซีดเรื้อรังในประเทศไทย วัตถุประสงค์ของการศึกษานี้เพื่อให้การวินิจฉัยภาวะผิดปกติทางหัวใจในผู้ป่วยเหล่านี้ก่อนที่จะมีภาวะหัวใจล้มเหลว

ผู้ป่วยและวิธีการศึกษา : ผู้ป่วยที่เข้ารับการศึกษาได้แก่ ผู้ป่วยเบต้าธาลัสซีเมียที่มาตรวจในคลินิกโรคเลือดตั้งแต่ 1 กรกฎาคม พ.ศ. 2542 ถึง 31 กรกฎาคม พ.ศ. 2543 ผู้ป่วยได้รับการตรวจร่างกาย เจาะตรวจเลือด และตรวจทางหัวใจ ได้แก่ เอกซเรย์ปอด คลื่นไฟฟ้าหัวใจและคลื่นเสียงสะท้อน หัวใจความถี่สูง (echocardiogram) ผู้ป่วยที่มีภาวะผิดปกติทางหัวใจได้แก่ ผู้ป่วยที่มีผล echocardiogram บ่งบอกถึงการทำงานของหัวใจผิดปกติ

ผลการตรวจ : พบว่ามีผู้ป่วย 26 ราย (ร้อยละ 12.3) มีความผิดปกติทางหัวใจ การตรวจคัดกรองโดยใช้เอกซเรย์ปอดที่พบว่าเงาหัวใจโตกว่าปกติ (CT ratio > 0.55) หรือตรวจคลื่นไฟฟ้าหัวใจผิดปกติ สามารถใช้วินิจฉัยความผิดปกติของหัวใจได้

สรุป : ในผู้ป่วยเด็กเบต้าธาลัสซีเมียควรมีการตรวจเอกซเรย์ปอดและคลื่นไฟฟ้าหัวใจเพื่อใช้ในการตรวจกรองภาวะความผิดปกติของหัวใจก่อนที่ผู้ป่วยจะมีอาการได้

คำสำคัญ : ธาลัสซีเมีย, หัวใจล้มเหลว

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