MEDWELL PUBLISHING
Research Journal of Biological Sciences 4 (2): 195-199, 2009
ISSN: 1815-8846

Cardiac Involvement in Patients with Transfusion Dependent β Thalassemia

[1]A. Azarkeivan, [2]A. Mehrvar, [3]M. Faranoush, [4]P. Vosough, [5]N. Mehrvar, [6]R. Ghorbani,
[7]A. Shahmohamadi, [8]M.A. Ehsani and [4]A.A. Hedayatiasl
[1]Department of Pediatric Hematologist-Oncologist,
Iranian Blood Transfusion Organization Research Center, Thalassemia Clinic Medical Doctor, Iran
[2]Department of Pediatric Hematologist-Oncologist, Army Medical University, Golestan Hospital, Iran
[3]Department of Pediatric Hematologist-Oncologist, Amir Al-Momeinin Hospital,
Semnan University of Medical Sciences, Iran
[4]Department of Pediatric Hematologist-Oncologist, MAHAK Children's Hospital,
Iran University of Medical Sciences, Iran
[5]Department of Molecular Microbiology, Islamic Azad University,
North Branch, Army Medical University, Iran
[6]Department of Biostatistics, Social Medicine, Semnan University of Medical Sciences, Iran
[4]Department of Pediatric Cardiologist, Iran University of Medical Sciences, Iran
[8]Department of Pediatric Hematologist-Oncologist, Tehran University of Medical Sciences, Iran

Abstract: Thalassemia is accounted as the most common hereditary anemia through our region. Appropriate therapy for this disease includes a regular monthly blood injection. However, in the approach patients will inevitably confront with side effects particularly iron overloads in critical organs including heart, ductless glands and liver. In this study, we wanted to consider the heart abnormalities in patients with β thalassemia, who received blood transfusion. In this study, 139 patients with β thalassemia (major and intermedia) enrolled, who referring to medical centers linked with the Iranian blood transition institute and Ali Asghar hospital. History about blood transfusion, iron chelation were taken. Physical examination were done too. Heart abnormalities have considered by echocardiography method. The mean (±SD) age was 21.1±7.1 years. Mean duration of treatment was 22.6±13.7 years. The 95.5% of patients had not respiratory problems. Mean (±SD) of ferritin was 1536.2±1609.6 ng dL^{-1}. The 26.5% had cardiac problems. In these patients, 4.3% had previous asthma, 12% complained from palpitation, 10% used drugs for their heart problems and at last 5.8% had cardiomegaly. In order to our results and previous researches we can say that heart can be considered as a primary site for iron deposition and alteration of heart abnormalities could be expected even in well chelated patients by echocardiography.

Key words: Echocardiography, heart abnormalities, iron overload, thalassemia, therapy, disease

INTRODUCTION

Thalassemia is a heterogeneity syndrome of a family of anemias (Piatti *et al*., 1999; Cracowski *et al*., 1998). This syndrome has deficient synthesis of one or more of the polypeptide chains of the normal human hemoglobin (Kanj *et al*., 2000; Levin and Koven, 1999; Tai *et al*., 1996). Transfusion dependent β thalassemia complicated by iron overload (Rametta *et al*., 1997; Ferrara *et al*., 2004).

β thalassemia affects a significant segment of the population in certain areas of the world (Vogel *et al*., 2003; Piomelli *et al*., 1974; Propper *et al*., 1980).

Treatment consists of multiple blood transfusions, a complication of which is iron overload (Aessopos *et al*., 2001). Over the course of the past 2-3 decades, hyper transfusion therapy has significantly increased the life expectancy and improved the quality of life of these patients (Aessopos *et al*., 2004). At the same time, there has been an increase in the frequency of complications of this therapy caused by iron overload (Aessopos *et al*., 2007). One of the toxic effects of iron overload is on heart and its function (Durongpisitkul *et al*., 2002; Mehrvar *et al*., 2008).

Corresponding Author: M. Faranoush, Department of Pediatric, Amir Al Momenin Hospital,
Semnan University of Medical Sciences, Semnan, Iran

Cardiac complications are a main feature of the clinical spectrum in transfusion dependent β thalassemia (Piomelli *et al*., 1974). They are the leading cause of death and have been well documented only in patients with thalassemia major (Ferrara *et al*., 2004). The prominent finding in this condition is Left Ventricle (LV) dysfunction, which is attributed mainly to iron overload, cardiomyopathy and leads gradually to cardiac failure and cardiogenic death (Vogel *et al*., 2003). Cardiac heart rate variability and cardiomyopathy is other cardiac complication (Kardelen *et al*., 2008). Although, patients with thalassemia major and thalassemia intermedia share common basic pathophysiological mechanisms, cardiac involvement may be different in the latter because patients with thalassemia intermedia live longer and generally have low hemoglobin levels and lower iron loads (Aessopos *et al*., 2004).

In this study, we survey cardiac complication in transfusion dependent β thalassemia.

MATERIALS AND METHODS

The place: The study was conducted, on adult Thalassemia clinic and Ali Asghar Children's Hospital in Tehran. The ethic committee of Iranian Blood Transfusion Organization approved the study.

Patients: A total of 139 cases were included in this survey. Data were collected from patients >7 years old during Jan 2004-2005. All of the patients had transfusion dependent β thalassemia (intermedia or major). Written informed consent was obtained from patients and parents or legal guardians in all cases. All of the patients received regular blood transfusions at 2-6 weekly interval to maintain hemoglobin levels above 9 g dL^{-1} and all had been treatment with desferioxamine. We ordered all of the convenient parameters for considering cardiac abnormalities. Also, for all of the cases, we determined the kind of their thalassemia, sex, age, ferritine level, Arterial Blood Gas (ABG) (before transfusion) and Chest X Ray (CXR), duration of blood transfusion and blood transfusion unit per months.

Methods: ABG were done but because of this painful procedure 112 patients did this examination and PO_2 and O_2 saturation were noted.

In CXR, we noted to 2 parameters: lung pattern and cardiac size. Cardiac function was mentioned by echocardiography measuring Left Ventilator Ejection Fraction (LVEF) and Fractionated Shortening (FS) according to method of teichholz. When the patient had history of cardiac disease and usage of cardiac drugs, we referred for special cardiac consult.

According to LVEF, we classified as normal (EF>70%), mild (EF = 50-69%) and cardiac problem (EF<50%).

Complete M-mode, 2-dimensional and Doppler (pulsed-wave, continuous-wave and color) echocardiography was performed at rest, using an Acuson 128 Computed Sonography System (Mountain View, CA) with 2.5-3.5 MHz transducers. All echo-Doppler studies were carried out by the same cardiologist and the tracings were interpreted by 2 independent cardiologists who were unaware of the patient data.

Statistical analysis: Statistical analyses were performed using chi square (χ^2) test and Spearman's correlation coefficient. The $p>0.05$ were considered statistically significant. All statistical analyses were performed with SPSS 11.5 for windows.

RESULTS

In this study, 139 patients enrolled, who were 104 (74.8%) patients with transfusion dependent β thalassemia major and 35 (25.2%) patients with thalassemia intermedia, respectively.

The mean (±SD) age was 21.2±7.1 year and also the mean (±SD) of treatment duration was 22.6±13.7. Most of the patients were in the range of 16-20 years old (37%). Clinical and laboratory results of patients showed in Table 1.

The 73.7% of patients used desferioxamine regularly. The mean (±SD) desferioxamine doses given to patients were 52.1±10.9 mg kg^{-1} in 5.4 days $week^{-1}$.

The mean (±SD) of serum ferritin was 15362±1609.6 ng dL^{-1}. There was a negative correlation between age and ferritin (r = -0.169, p = 0.045) (Table 2).

Data showed that 95.5% of patients (128) had no respiratory symptoms but 4.5% of patients complained from respiratory symptoms, which most of them was asthma. There was abnormal Pulmonary Function Test (PFT) in 72.7% as restrictive pattern and in 2.3% as combined pattern (Table 1 and 3).

The 85 patients (62.8%) had normal liver size and other had mild to moderate hepatomegaly. Twenty six patients (19.4%) had normal spleen and 74 patients (55.2%) were splenectomized.

In ABG, the mean±SD of PO_2 was 73.5±17.9 mmHg and median was 73.4 mmHg and the mean ±SD of O_2 saturation was 90.7±11.5% and median was 94%.

In CXR that were done for 112 patients 88 patients (78.6%) had normal heart size and only 8 (7.2%) had cardiomegaly.

Table 1: Clinical and laboratory results of patients

Variable	n	(%)
Cardiac problem		
+	36	26.5
-	100	73.5
Desferioxamine usage status		
Regular	101	73.7
Irregular	33	24.1
No use	3	2.2
CXR finding		
Normal	72	63.7
Intrmediate	24	21.2
Severe	17	15.0
Spleen size		
Normal	26	19.3
Splenctomized	75	55.6
>4 cm	34	25.2
Respiratory problem		
+	6	4.5
-	128	95.5
Pulmonary function test		
Normal	34	25.6
Restrictive	96	72.2
Mixed	3	2.3
History of cardiac problem		
+	6	4.4
-	129	95.6
Bone disease		
Normal	29	20.9
Mild	57	41.0
Severe	53	38.1
Secondry sexual development		
-	65	46.8
Intermediate	10	7.2
+	64	46.0

Table 2: Distribution of Ejection fraction, ferritin and LVEDV with respect to age in β thalassemia patients

	Age (year)			
	<20		≥20	
Parameter	N	(%)	N	(%)
Ejection fraction				
<50	4	5.5	9	13.4
50-69.9	55	75.3	47	70.1
≥70	24	19.2	11	16.4
Feritin				
<1000	29	39.7	38	56.7
1000-2500	32	43.8	21	31.3
>2500	12	16.4	8	11.9
LVEDV*				
<3.5	1	1.4	4	6.3
3.5-4.5	25	34.7	21	33.3
>4.5	46	63.9	38	60.3

*LVEDV: Left End Diastolic Ventricular Volume

The 26.5% of patients had history of cardiac disease as below: 12% palpitation, 10% used cardiac drugs and 7.2% cardiomegaly. Distribution of ejection fraction, ferritin and LVEDV with respect to age in β thalassemia patients showed in Table 2.

The mean±SD of Ejection Fraction (EF) was 60.3±9.7 (30-80%) and only 9.3% of patients had EF below 50%. About 17.9% of patients had EF>70 and 72.9% patients had EF between 50-69%. There was significant negative correlation between age and EF ($p = 0.044$, $r = -0.17$) (Table 2). The mean±SD of left end diastolic ventricular volume was 4.7±0.6 (2.9-6.0 mm^3). There wasn't any correlation between age and left end diastolic ventricular volume ($p = 0.819$, $r = 0.020$) (Table 2). But there was significant correlation between EF and left end diastolic ventricular volume ($p = 0.001$, $r = 0.431$). Table 3 showed distribution of ejection fraction, ferritin and LVEDV respect to spleen size in β thalassemia patients.

Table 3: Distribution of Ejection fraction, Ferritin and LVEDV with respect to spleen size in β thalassemia patients

	Spleen size					
	Normal		Splenctomized		>4 cm	
Parameter	N	(%)	N	(%)	N	(%)
Ejection fraction						
<50	1	3.8	11	14.7	1	2.9
50-69.9	20	76.9	54	72.0	25	73.5
≥70	5	19.2	10	13.3	8	23.5
Feritin						
<1000	7	26.9	42	56.0	16	47.1
1000-2500	16	61.5	21	28.0	13	38.2
>2500	3	11.5	12	16.0	5	14.7
LVEDV*						
<3.5	0	0.0	5	7.1	0	0.0
3.5-4.5	11	42.3	19	27.1	14	41.2
>4.5	15	57.7	46	65.7	20	58.8

*LVEDV: Left End Diastolic Ventricular Volume

DISCUSSION

These data show that only 4.3% of considered patients had asthma, 5.8% showed cardiomegaly and at last only 12% complaint from heart abnormalities. There was a significant difference between the duration of blood transfusion unit and iron overload ($p<0.01$).

Aessopos *et al.* (2001) considered 880 patients with β thalassemia, who 5.4% had cardiac abnormalities, 13.6% had left ventricle failure and only 7.2% had right ventricle abnormalities. They concluded that cardiac abnormalities in patients with β thalassemia can be a result of iron overload in this organ.

In one study, Ferrara *et al.* (2004) on patients with β thalassemia (major and intermedia), they said that patients with thalassemia intermedia show more left ventricle failure than patients with thalassemia major. They concluded that this hypothesis needs more research.

Vogel *et al.* (2003), did echocardiography method on 52 patients with β thalassemia and their results were as 73% of patients had iron overload that 23 patients showed left ventricle abnormality. They concluded that existence of cardiac failure in patients with transfusion dependent β thalassemia is because of iron overload in this organ and echocardiography is a suitable method for diagnosis these failures.

In another study, Aessopos *et al.* (2004), they assessed cardiac status by echocardiography in 202 patients with thalassemia major who had been treated in a standard way since their early infancy with intensive transfusions and desferioxamine chelation therapy and who had good compliance with this regimen. Their conclusion was as strict lifelong adherence to the standard transfusion and desferioxamine therapy reduces considerably the occurrence of heart failure, LV dysfunction and pericarditis, prevents early heart failure and pulmonary hypertension, but does not eliminate completely cardiac disease in patients with thalassemia major.

Again in another study, Aessopos *et al.* (2007), compared a number of parameters derived from Echo to cardiac failure in 142 thalassaemia major patients, who had undergone a cardiac magnetic resonance study. They concluded that echo parameters for cardiac failure prediction have restricted value, whereas CMR is essential to assess cardiac failure. However, patients with decreased LV systolic function should be considered a priori as having cardiac failure and chelation therapy should be intensified.

Durongpisitkul *et al.* (2002) determined variables associated with cardiac involvement in asymptomatic β-thalassemia patients. They showed that in asymptomatic β-thalassemia children, chest X-ray and ECG should be used for screening patients for the detection of cardiac involvement.

CONCLUSION

According to these data and other studies, we can say that cardiac failures in patients with transfusion dependent β thalassemia can have correlation with the age of patients. Because the patient's age show the duration of blood transfusion and is a sign of blood transfusion unit, iron overload and it's effect on cardiac function.

These results show that doctors by echocardiography method can diagnose cardiac abnormalities in patients with β thalassemia.

There can be significant difference between cardiac abnormalities and the duration of blood transfusion. That can be because of iron overload in this organ. Another reason can be because of chronic fluid overload in patients during blood transfusion.

Serum ferritine level, however have been found to have direct correlation to iron deposition, in the liver 15 but in the other hand, it is an acute phase protein as well as a product of hepatocellular damage, thus infection, congestive heart failure and hepatitis can lead to increased level and may be mistake with the iron body store in thalassemic patients. So, it isn't an ideal value for assessment of iron body store.

At last, we can say that heart can be considered as a primary site for iron overload and alteration of cardiac function could be expected even in well chelated patients. So, it may be needed to regulatory follow up especially by echocardiography.

ACKNOWLEDGEMENT

Adult thalassemia clinics, Hematology ward Ali Asghar Children's hospital.

REFERENCES

Aessopos, A., A. Giakoumis, C. Fragodimitri, F. Karabatsos, A. Hatziliami, J. Yousef, E. Gotsis, V. Berdoukas and M. Karagiorga, 2007. Correlation of echocardiography parameters with cardiac magnetic resonance imaging in transfusion-dependent thalassaemia major. Eur. J. Haematol., 78 (1): 58-65.

Aessopos, A., D. Farmakis, A. Hatziliami, C. Fragodimitri, F. Karabatsos, J. Joussef, E. Mitilineou, E. Diamanti-Kandaraki, J. Meletis and M. Karagiorga, 2004. Cardiac status in well-treated patients with β-thalassemia major. Eur. J. Haematol., 73 (5): 359-366.

Aessopos, A., D. Farmakis, M. Karagiorga, E. Voskaridou, A. Loutradi, A. Hatziliami, J. Joussef, J. Rombos and D. Loukopoulos, 2001. Cardiac involvement in β-thalassemia intermedia: A multicenter study. Blood, 97 (11): 3411-3416.

Cracowski, C., B. Wuyam, V. Klein and P. Levy, 1998. Lung function and exercise capacity in β-thalassemia major. Eur Respir. J., 12 (5): 1130-1136.

Durongpisitkul, K., S. Kruasukon, C. Kangkagate and V.S. Tanphaichitr, 2002. Early detection of cardiac involvement in β-thalassemia children. J. Med. Assoc. Thai, 85 (Suppl 2): S667-673.

Ferrara, M., S.M. Matarese, B. Borrelli, A. Perrotta, G. Simeone, N. Greco, D. Iarussi and L. Esposito, 2004. Cardiac involvement in β-thalassemia major and β-thalassemia intermedia. Hemoglobin., 28 (2): 123-129.

Kanj, N., A. Taher and A. Shamseddien, 2000. Relation of serum ferritin level to polmonary function in patients with thalasseima major and the acute effects of transfusion. Eur. J. Haematol., 64 (6): 396-400.

Kardelen, F., G. Tezcan, G. Akcurin, H. Ertug and A. Yesilipek, 2008. Heart rate variability in patients with β-thalassemia major. Pediatr. Cardiol., 29 (5): 935-939.

Levin, C. and A. Koven, 1999. Pulmonary Function in β-thalassemia Patients β-thalassemia Congress Malta 1997, 5-10 April Wintrobe's Clinical Hematology. 10th Edn. Lea and Febiger. Philadelphia the β-thalassemia and Related Disorder, pp: 1405-1448.

Mehrvar, A., A. Azarkeivan, M. Faranoush, N. Mehrvar, J. Saberinedjad, R. Ghorbani and P. Vosough, 2008. Endocrinopathies in patients with transfusion-dependent β-thalassemia. Pediatr. Hematol. Oncol., 25 (3): 187-194.

Piatti, G., L. Allegra, U. Ambrosetti, M.D. Cappellini, F. Turati and G. Fiorelli, 1999. β-thalassemia and pulmonary function. Haematologica, 84 (9): 804-808.

Piomelli, S., M.H. Karpatkin, M. Arzanian and M. Zamani *et al*., 1974. Hypertransfusion regimen in patients with Cooley's anemia. Ann. N.Y. Acad Sci., 232: 186-192.

Propper, R.D., L.N. Button and D.G. Nathan, 1980. New approaches to the transfusion management of β-thalassemia. Blood, 55 (1): 55-60.

Rametta, F., De michele and S. Buffardi, 1997. β-thalassemia Major: Pulmonary Involvement β-Thalassemia Congress Malta.

Tai, D., Y. Wang, J. Lou and W. Wang, 1996. Lungs in β-thalassemia major patients receiving regular transfusion. Eur. Respir., 9 (7): 1389-1394.

Vogel, M., L.J. Anderson, S. Holden, J.E. Deanfield, D.J. Pennell and J.M. Walker, 2003. Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial dysfunction related to myocardial iron overload. Eur. Heart J., 24 (1): 113-119.