Prevalence of Cardiac Dysfunction among Thalassaemic Patients in Babylon Governorate

Ahmed Shemran Metleq AL-Watify , Mudher Hassan Noor , Sabeeh Salih Al-Fatlawy
Babylon University, College of Medicine Dept. of Surgiry

Abstract

A prospective study was conducted on 216 patients with thalassaemia classified as 135 patients with β-thalassaemia major, 57 patients with thalassaemia intermedia and 24 patients with sickle cell/ thalassaemia, who were attending the thalassaemia center at Babylon Maternity and Children Hospital, from period of August 2003 to April 2004. Their age ranged from (1- 30) years with a mean of 11.28 years. They were studied for cardiac dysfunction, 39 patients (18%) were found to have cardiac abnormality classified as (43.7%) as asymptomatic patients, (33.3%) as asymptomatic heart failure, and (23%) as asymptomatic heart failure. Risk factors for cardiac dysfunction were:

1. Age older than 10 years.
2. Frequent blood transfusion more than 120 times.
3. Serum ferritin more than 1800 - 2000 ng/L.

الخلاصة

تم إجراء هذه الدراسة في مركز فقر الدم الوراثي في مستشفى بابل للولادة والأطفال ، للفترة ما بين شهر آب لسنة ٢٠٠٣ لغاية شهر نيسان لسنة ٢٠٠٤ على المرضى المصابين بفقر الدم البحري (فقر الدم البحري الكبير من نوع B (B-thd. Major) ، فقر الدم البحري المتوسط (Thalass. intermedia) فقر الدم البحري المنجلي (sickle cell thalass.) فوجد أن تسع وثلاثين حالة (١٨%) يعانون من مشاكل في وظائف القلب من بين (٢١٦) حالة مسجلة في المركز ، وكما صنفت على النحو التالي :

١.(٤٣,٧) (a symptomatic): اضطرابات في وظائف القلب والملاحظ في جهاز الايكو فقط (لا يوجد أعراض مرضية) .

٢.(٣٣,٣) (a symptomatic heart failure): يعانون من مشاكل القلب كتضخم عضلة القلب والملاحظ من أشعة الصدر والايكو وتخطيط القلب (بدون أعراض مرضية) .

٣.(٢٣%) يعانون من فشل القلب (مع ظهور الأعراض المرضية لعجز القلب) .

وكما وجدَ أيضاً إن عوامل خطر الإصابة تزداد في الحالات التالية :

١.إذا كان عمر المريض أكثر من عشر سنوات .

٢.عدد مرات إعطاء الدم أكثر من (١٢٠) مرة .

٣.نسبة كمية الحديد أكثر من (١٨٠٠ – ٢٠٠٠ مايكروغرام / اللتر) .

Introduction

The commonest haemoglobin pathies (Hb-Pathies) that need frequent interval, regular blood transfusions are α and β thalassaemia and sickle cell/thalassaemia [1], where regular blood transfusions eliminate the complications of anaemia and compensate bone morrow expansion, permit normal development through out life and extend survival [2].

In parallel, transfusion result in a second disease while treating the first , that is of inexorable accumulation of tissue iron that without treatment, is fatal in the second decade of life [2].

A recent study found that a (15%) extension of transfusion interval during administration of neocytes concentration, expected to minimally reduce the requirement of iron chelation therapy but the cost of an increased exposure to donated units and five fold increments in preparation expenses over those of standard concentration [2].

In absence of early diagnosis and treatment of thalassaemia, most patients die before the age of 5 years [3], but life expectancy and quality of life for those born with thalassaemia major has improved greatly in the last 20 years in countries with access to safe blood transfusion and active iron chelation therapy with desferrioxamine [4].

Nevertheless, cardiac symptoms and premature death from cardiac complications are still the major problem and is considered a leading cause of morbidity and mortality [3].

Cardiac disease is secondary to either chronic severe anaemia or from iron overload [3, 5, 6, 7], chronic sever anaemia can be corrected by hypertransfusion regimen, while iron

overload can be corrected by adequate chelation therapy to remove the iron from tissue, otherwise iron accumulation is considered fatal [3, 8].

Cardiac cell are particularly sensitive to free oxygen radicals (hydroxyl-radical [9] and lipid peroxidation [10]) which are caused by iron deposition and makes myocytes lose their characteristic pattern of beating [11].

Desferrioxamine is a powerful iron chelator that binds iron and prevents generation of reactive oxygen species and restore normal cellular activity [11].

Also cardiac lesion may occur from reperfusion injury, coronary atherosclerosis [12] and from alteration of systolic and diastolic properties of left and right ventricle [13].

The heart complications induced by iron overload [3] remained responsible for (70%) of deaths in thalassaemia [7] and these complication include:

1. Congestive dilated cardiomyopathy (most common problem) [14].
2. Arrhythmias occur through deposition of iron in the bundle of His and Purkinje system [15].
3. Pericarditis.
4. Sudden death or death from progressive congestive heart failure [3].

These problems typically occurs in the absence of symptoms [16], development of symptoms of heart failure imply advanced disease with a poor prognosis [3, 16]. Therefore, regular assessment of cardiac status recognizes early stages of heart problems and allow for prompt intervention [3].

Besides medical history and physical examination, the basic cardiological assessment should include electrocardiograph, chest x-ray, and echocardiograph (which is considered a useful non-invasive diagnostic tool and correlate roughly with the number of blood transfusion) [17].

The frequency of cardiological assessment depends on [3]:

1. Age of patients.
2. The presence and severity of cardiac complications as follows:

a. Asymptomatics, well chelated patients , with normal heart: every year after (10 - 15) years of age.

b. Asymptomatics with moderate cardiac impairment : every (6 – 8) months.

c. Symptomatics patients with severe cardiac impairment: every (1 – 4) month.

Aim of Study

This study was carried out to determine:

1. The prevalence of cardiac dysfunction among thalassaemic children in Babylon Governorate.
2. The correlation of cardiac dysfunction with certain variables including age, number of blood transfusion, serum ferritin and type of thalassaemia.
3. Cardiac dysfunction classified according to echocardiograph, chest x-ray, electrocardiograph, in addition to sign and symptoms of heart failure .

Patients and Methods

Patients:

A total of (216) patients with thalassaemia and sickle cell/ thalassaemia. ((135) patients with β-thalassaemia major, (57) Patients with thalassaemia intermedia and (24) patients with sickle cell/ thalassaemia)) , who were attending the Thalassaemia Center at Babylon Maternity and Children Hospital from the period of August 2003 to April 2004 were included in the study, their age ranged from (1 – 30) years with a mean of (11.28) years.

II- A detailed history and clinical examination was obtained for every patient.

III- All patients were investigated by:

1. Chest X-ray.
2. Electrocardiograph.
3. Echocardiograph (Data on right and left heart dimension and biventricular function were obtained).
4. Blood samples were obtained from all patients and sent for measuring serum ferritin.

Statistical Analysis

The statistical analyses utilized were fisher exact test and t-test. P-value of less than 0.05 is considered to be significant and of less than 0.01 is considered to be highly significant

Results

Table 1 Distribution of patients with cardiac dysfunction among total patients.

Total No. of patients	*+ve cases		*- ve cases	
	No.	%	No.	%
216	39	18	177	82

P value < 0.01

*(+ve = positive, -ve = negative)

Frequency of cardiac dysfunction is highly significant among total patients

Table 2 Comparison of positive, negative cases to number of blood transfusion.

Total No. of patients	+ve cases		- ve cases	
	No.	No. of blood trans. (mean ± SD)	No.	No. of blood trans. (mean ±SD)
216	39	100.5 ± 37	177	29.57 ± 20.5

P value < 0.01

Cardiac dysfunction is increased with increasing number of blood transfusion and this result was statistically is highly significant.

Table 3 Age distribution of positive and negative cases

Age	+ ve cases		- ve cases		Total	
	No.	%	No.	%	No.	%
< 5 years	0.0	0.0	50	100	50	100
5 - 10 years	4	6.8	54	93.2	58	100
> 10 years	35	32.5	73	67.5	108	100
Total	39		177		216	

P < 0.01

There is highly significant increased of cardiac dysfunction in thalassaemia patients with increasing age of patients.

Table 4 Distribution of cases according to type of thalassaemia

Type of thalassaemia	+ ve cases		- ve cases		Total	
	No.	%	No.	%	No.	%
β-thalassaemia	24	17.7	111	82.3	135	100

Thal. intermedia	11	19.2	46	8o.8	57	100
Sickle cell thalassaemia	4	16.6	20	83.4	24	100

P > 0.05

There is no statistically significant of cardiac dysfunction among types of thalassaemia.

Table 5 Distribution of cases according to number of blood transfusion and type of thalassaemia

Type of thalassaemia	+ ve cases		- ve cases		
	No.	No. of blood trans. (mean ± SD)	No.	No. of blood trans. (mean ± SD)	P value
β-thal. major	24	116 ± 9.5	111	43.63 ± 8.1	< 0.01
Thalassaemia intermedia	11	80 ± 3.95	47	35. 82 ± 6.7	< 0.01
Sickle cell thalassaemia	4	65 ± 4.08	19	26.42 ± 14.9	< 0.01

P value < 0.01

Number of blood transfusion in positive cases is significantly higher than negative cases in each type of thalassaemia.

Table 6 Distribution of cases according to level of serum ferritin

Cases	Serum ferritin ng/L
+ ve cases - ve cases	> 1800 - 2000 < 1800

Cardiac dysfunction is increased with increasing serum ferritin (of more than 1800 - 2000 ng/L).

Table 7 Distribution of cardiac changes in positive cases

+ve cases		Echo	ECG	CXR	Severity of heart problem
No.	%				
17	43.7	Abnormal (mild dysfunction) systolic or ± diastolic dysfunction	Normal	Normal	Asymptomatic patient

13	33.3	Abnormal Echo with mild dilatation of both LV & RV	Abnormal	Mild cardiomegally	Asymptomatic heart failure
9	23	Abnormal with severe dilatation of both LV & RV *	Abnormal ECG with enlargement chamber	Huge Cardiomegally	Symptomatic heart failure

* LV: left ventricle.

RV: right ventricle.

P value > 0.05

No significant difference of cardiac dysfunction cases among total positive cases.

Discussion

A Blood transfusion is necessary for survival of patients with thalassaemia, but may cause myocardial dysfunction due to myocardial siderosis [18], where congestion cardiomyopathy is most common defect that occurs with iron overload [2], but other problems may happen in including arrhythmia and pericarditis [13].

Cardiac complications were considered a common cause of thalassaemic patients in (70%) of deaths [7] and intensive chelation therapy with desferrioxamine can prevent cardiac complications [5, 6] and may reverse deleterious effects of severe iron overload which becomes a problems only with advance in technology that have prolonged life and made feasible repeated blood transfusion.

The results of our study show that (18%) of thalassaemic children had cardiac dysfunction which is compatible to other study done in Iraq in Al-Karama Teaching Hospital [19]. This similarity in results resulted from same facilities for checking and follow up in both centers.

High percentage of cardiac problems my be due to poor education and poor compliance of many patients to receive desferrioxamine therapy and used also low-transfusion regimen because of unavailability of blood and desferrioxamine pump occasionally.

The prevalence of heart abnormality was directly related to the number of blood transfusion.

Positive cases associated with more than (100) times of blood transfusions, in contrast to negative cases which were transfused between (25 – 35) times. This indicates a strong correlation between the cumulative number of blood transfusion and functional cardiac derrangement in children with thalassaemia [20].

This is because of higher number of blood given associated with higher risk of haemosiderosis which makes the iron precipitate on multiple organs including heart.

There was no significant difference of cardiac dysfunction among all types of thalassaemia. Either because of small number of patients with thalassaemia intermedia and sickle cell/thalassaemia, in comparison to slightly higher number of patients with β-thalassaemia major. Also β-thalassaemia major depends comple-tely on blood transfusion to save life, while thalassaemia intermedia depends on increased absorption of iron from the intestine to maintain haemoglobin level between (6 – 9) gm/dl even without blood transfusion [3].

In sickle cell / thalassaemia, cardiac problem may be due to cardiac siderosis and ischaemic cardiac myopathy. This explains why patients of β-thalassaemia major with heart abnormality associated with higher number of blood transfusion (of more than 116 times); in comparison, to patients with thalassaemia intermedia and sickle cell/thalassaemia, were (80) and (65) time respectively.

The prevalence of cardiac dysfunction increased with increasing age ranged from (0.0%) of those less than (5) years of age to (6.8%) of those between (5 – 10) years and (32.5%) above (10) years of age from total positive and negative patients.

This can be attributed to increase number of blood transfusion as children getting older due to increase growth, development of antibody to red blood cells, possibly developing of hypersplenism and emergence of disease like diabetic mellitus, hypoparathyroi-dism.

Also, the current study had revealed that all cases with heart problems associated with serum ferritin level of more than (1800 – 2000) ng/l which compatible to study done in England [21]. This explained that higher ferritin results in high level of unbound iron which generate reactive harmful oxygen metabolites and toxicity [22] leading to greatly increased risk of cardiac disease and

early death and those patients are candidates for continuous intravenous ambulatory desferrioxamine [23] and to avoid this complication, early assessment of myocardial iron loading by (magnetic resonance imaging T2) which is sensitive to low level of iron loading, highly reproducible which allows longitudinal assessment over time and can be repeated indefinitely because it is non- invasive [24, 25].

Also our study shows distribution of cardiac changes that (43.7%) classified as asymptomatic patients, (33.3%) as asymptomatic heart failure and only (23%) of total positive cases classified as symptomatic heart failure. This indicates that the physical examination is surprisingly normal even in patients with heavy cardiac iron deposition. Once the evidence of cardiac failure appears, the heart function rapidly deteriorates often without response to medical intervention. Therefore, regular assessment of cardiac status by using echocardiography which the most useful non-invasive diagnostic tool of cardiac abnormality [17] and early chelation therapy prevent cardiac dysfunction in patients with iron overload.

Conclusion

1.This study has revealed that the prevalence of cardiac dysfunction among thalassaemia children was (18%) and the rate is similar to other study done in other centers of Iraq.

2.The prevalence of cardiac dysfunction was directly related to number of blood transfusion, age of patients and serum ferritin level.

3.Cardiac dysfunction is surprisingly asymptomatic even with sever cardiac siderosis (only 23% of total positive cases have a feature of frank sign and symptoms of heart failure).

Recommendations

1.Bone marrow transplantation and hopefully gene therapy should be available to prevent organ siderosis.

2.All thalassaemia patients should be assessed regularly for heart abnormality by echocardiograph.

3.On splenectomy, liver biopsy should be taken to measure iron concentration as an indirect way of cardiac siderosis.

4.Because serum ferritin is affected by a whole host of different factors and is an unreliable maker; therefore, it is best to do indirect non-invasive assessment of myocardial iron by (magnetic resonance imagine T2).

References

1.Antonio C., 1997, Thlass. International Federation, First edition, 5.

2.Nancy T. Olivieri and Gary M. Brittenham., 1997, Blood, Vol. 89, No. 3, (February 1), 739.

3.The Management of the cardiac complications of thalass. major; Guidelines for the Clinical Management of Thalassaemia. Thalass. International Federation; April 2000; 1.

4.John B. Porter. Novartis Pharma. Verlag., 1999, 9.

5.Paul J. Scott. Hemoglobin path, in, Behraman RE, Kliegman RM, eds. Nelson Textbook of Pediatrics, 1996, 15th ed., Philadelphia, WB Saunders, 1396.

6.Vullo R., Geogranda E. What is thalassaemia?, 1995, Second edition. Thalass. International Federation, Cyprus, 5.

7.Toronto A. Deferiprone provides greater cardiac protection in thalass. May 7, 2003.

8.Modell B, Khan N., Darlism M. , 2000, Lancet, 355, 2051.

9.McCord JM, (1993), ,clinical biochemistry, 76, 351.

10. Enright H. U, Millerwj, Hebbl RP. Nucleosomal histone protein protects DNA from iron mediated damage. 1992, Nucleic Acids Research, 20, 3341. Farber JL. Mechanism of cell injury activated O_2 species. 1994, Environ. Health Perspect. 102, 17.

11. Link G. Konijn AM, Hershko G. (1999), J. Lab. Clin. Med. 133, 179.

12. Horwitz LD, Rosenthal EA. , Vascular medicine, 1999, 4 (2), 93.

13. Mariottie E, Agostini A, Angeluces E, *et al*. , 1993, Bone marrow transplant, 12 Suppl . 1214.

14. Liu, P., and Olivieri, N. , 1994, Cardiovascular Drugs Therapy, 8, 101.

15. Olson, L. *et al*. , 1987, J. Am.Col. Card., 10, 1239.

16. Rahko, P., Salevui, *et al*, 1986, J. Am.Col. Card.,, 8, 436.

17. Leon M., Borer, J. *et al* 1979, New Eng. J.Med., 301, 1143.

18. Kuek NO, Aras G, Sipathi T, *et al*. , 1999, Ann. Nucl. Medic. June,13 (3) , 175.

19. Al-Naqeeb Waffa. Cardiac complications of thalass. Al-Karama Teaching Hospital (Iraq, Baghdad). 2002, The First Scientific Conference on Thalassaemia Hb-pathy.

20. Scopinaro F, Banci M, *et al*. (1993). , 1993, Euro. J., 20, 603.

21. Olivieri NF, Nathan DG, *et al*.,1994, New Eng. J.Med, 331, 574.

22. Long JAJ, Doppman JL *et al*,1980 (Medicine), J. Comput. Assist. Tomograph. 4, 159.

23. Berriman AM, Davis SA, *et al*, 1992 (Medicine), Am. J. Hematol. 41, 61.

24. Anderson, Dudley., 2003, Hematol., 481.

25. Anderson, Holdens S, Davis B., *et al.* , 2001, Euro Heart. 22, 2171.