

Survival and Disease Complication of Thalassemia Major: Experience of 14 Years at King Abdulaziz University Hospital, Jeddah, KSA

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Abstract. Treatment of thalassemia major is complex, expensive and requires a multidisciplinary approach. Optimal clinical care is demanding and expensive, but achievable. To assess the prevalence of survival and disease complications among patients with thalassemia major treated at our center; a retrospective chart review was done of all patients followed and treated at King Abdulaziz University Hospital with a diagnosis of Thalassemia Major from 1990-2004. A total of 360 patients (203 males & 157 females) were transfusion dependant since early childhood and treated with parenteral Deferoxamine. Out of 360 patients, 293 (90.29%) patients were alive, 27 (7.2%) patients had died, 15 (4.2%) patients underwent BMT and 25 (6.9%) patient' follow-up were lost. Twelve (3.3%) patients died from heart disease. 7 (1.9%) patients died from infections, all patients were splenectomized. The serum ferritin levels for patients who died were significantly higher than for those patients who survived (7,500 vs. 3, 200; $p < 0.001$). Cardiac constitutes the first important cause of death followed by infection. Complications and deaths among thalasseemics is iron related organ dysfunction and age related. The majority of complicated patients were on non-optimal chelation therapy and non-compliance.

Keywords: Thalassemia major, Survival, Disease complication, University hospital, KSA

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Introduction

Dramatic improvements in the clinical management of thalassemia major over the last 10-20 years have led to an impressive increase in the lifespan and the improve quality of life^[1]. The prognosis of patients with transfusion dependent thalassemia major has been improved by regular transfusion and iron-chelation therapy with deferoxamine^[2-7].

This report presents the result of disease complication and causes of death in patients with thalassemia major, who were followed and treated at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia over the last 14 years. Furthermore, it assesses the prevalence of survival, and their present clinical status to define the prognosis in this group of complex patients.

Methods

A retrospective chart review was done of all patients with thalassemia major followed and treated at KAUH in Jeddah, Saudi Arabia between 1990 and 2004. University Hospital, an academic tertiary care medical center, in which most of the cases followed, was referred mainly from different hospitals in Jeddah, Makkah and from different cities from the Western region of the country.

The retrospective data for this report were collected by means of specially prepared forms from hematology clinic, day care, patient cards and medical records during the time period from January 2002 through December 2004.

A total of 360 patients (203 males and 157 females) were treated and followed during the 14 years as seen in Fig. 1. The majority of these patients were homozygous β -thalassemia major and less than 2% were compound HbE β o thalassemia. All were transfusion dependent since early childhood and treated with parental Deferoxamine.

The pre-transfusion hemoglobin level was maintained between 9-10 g/dL in all the patients. Thalassemia intermedia were excluded from this analysis as well as patients with successful engraftment of transplanted stem cell.

Disease complications were assessed by measuring iron overload through assessment of iron balance, and the mean of serum ferritin

concentration for all patients yearly. All patients were tested for Hepatitis B & C; any seropositive patients were referred to hepatologist for follow-up and treatment.

Other complications including cardiac, endocrine, bone diseases and others were recorded from the annual referred sheet. Complicated cases were referred to different subspecialties for treatment.

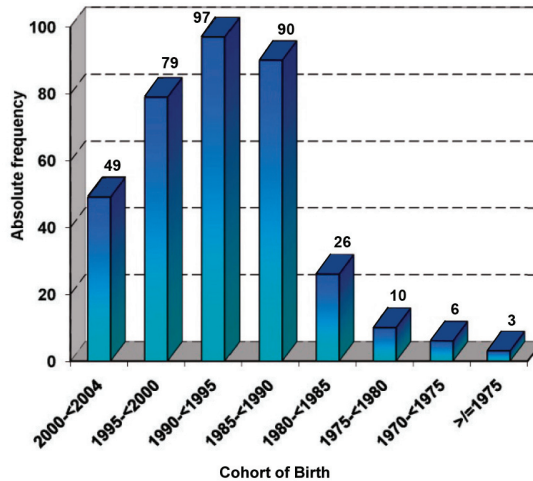


Fig. 1. Distribution of cohort by birth in all the studied thalassemia major (360 cases) at KAUH, Jeddah, KSA.

Statistical Analysis

Using SPSS program, V-10 under Windows, the descriptive statistics for continuous variables were done by calculating mean, standard deviation (\pm SD), standard error of mean (\pm SEM), median and range. For qualitative data, description was done by calculating numbers and percent. Analysis for quantitative data was done by “student’s” *t* test. Wilcoxon rank-sum test, (*Z*) was performed for nonparametric analysis. Results were considered significant at $p < 0.05$. Probability of survival curve as described by Kaplan-Meier method. Graphic representation was done using HGW program.

Results

Out of 360 patients (203 males and 157 females) initially enrolled in the study; the median patient age was 12.50 years (range, 1-32 years).

The majority of patients referred to KAUH after the age of 12 years. Twenty-five (6.9%) encountered lost follow up. Fifteen patients (4.2%) underwent successful stem cell transplant. Twenty-five percent (25%) of patients had undergone splenectomy at median age of 8 years (range, 2.5 – 16 years).

Table 1 summarizes the patients' clinical characteristics and disease complications by age group which shows that most of the complications are age related and iron overload.

Table 1. Complication of thalassemia major by age group.

	0-10y (n=99), %	11-20y (n=150), %	21-30y (n=26), %	>30y (n=3), %	Overall (n=278), %
Serum ferritin (ng/ml)					
Mean \pm SD	2100 \pm 512.6	4920 \pm 2024.1	4104.8 \pm 1298.4	4127.3 \pm 1211.7	3272.5 \pm 1574.8
Range	1580-3200	2500-12600	3200-6000	3100-5500	1580-12600
Median	2115	4850	4290	3900	4250
Hepatitis C	3 (3.0%)	42 (28%)	17 (65.4%)	2 (66.7%)	64 (23.0%)
Hepatitis B	2 (2.0%)	6 (4%)	6 (23.0%)	1 (33.3%)	18 (6.5%)
Heart disease requiring treatment	0	1*	5	3	9
Liver failure/cirrhosis	0	0	1	1	2
Endocrine disorders:					
-Thyroid disease	0	1	3	1	5
-Hypoparathyroidism	0	4	5	2	11
-Diabetes Mellitus	0	3	8	2	13

* 16 years old female patient

The median serum ferritin 4250 (range, 1580-12600), the median ferritin measurement had increased with age.

Of 278 patients tested for Hepatitis C viruses (HCV) 23% were seropositive, the risk increases with age 3% below age of 10 years and 66.7% with the age 30 years and above.

Organ dysfunction due to iron overload was common in adolescents and young adults; majority of complications started after 10 years of age.

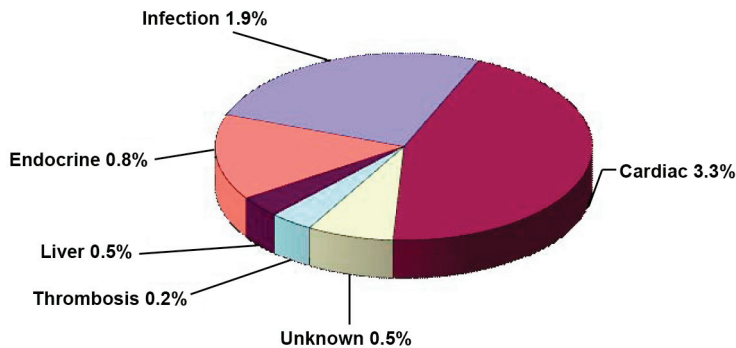
No patients age 15 years or younger were reported to have heart disease requiring treatment.

Twenty-seven patients (7.2%) died, and 251 (90.29%) survived.

Table 2 and Fig. 2 summarize the cause of death and patients clinical characteristics.

Table 2. Summary of the causes of death and patient clinical characteristics in 278 patients with TM treated at KAUH.

Causes of death	Number (%)	Age (Yrs)		Serum Ferritin (ng/ml)		
		Mean + SD	Range	Mean ± SD	Median	Range
Cardiac	12 (44%)	19.0 ± 2.98	16-24	7645 ± 3404	7750	3000-12600
Infection	7 (26%)	14.14 ± 2.61	10-18	2314 ± 296	2400	1800-2600
Endocrine	4 (15%)	23.0 ± 1.83	21-25	6375 ± 2206	6500	3600-8900
Liver	1 (4%)	28.0 ± 0	--	4000 ± 0	--	--
Thrombosis	1 (4%)	17.0 ± 0	--	3500 ± 0	--	--
Unknown	2 (7%)	19.0 ± 1.41	18-20	3000 ± 707	3000	2500-3500
Total	27 (100%)	18.59 ± 4.21	10-28	5442 ± 3346	4000	1800-12600

**Fig. 2. The incidence of death in patients with thalassemia major between 1975-2000 treated at KAUH, Jeddah, KSA.**

Twelve patients (3.3%) died from heart disease; seven patients (1.9%) from infections and all were splenectomized.

Three (0.8%) died from endocrine disorders, two (0.5%) from liver disease and two (0.5%) had multiple organ dysfunction. One patient died from thrombosis.

On comparing, survived versus death cases regarding serum ferritin, it was found that the mean of serum ferritin in survived cases was 3009.32 ± 1143.29 , median = 2590.0; while in death cases they were 5442.59 ± 3346.54 , median = 4000.0. There was highly significant

difference between both groups being higher in death cases with $Z = 3.7$, $p < 0.001$.

The median serum ferritin in death cases was 4000 (range, 1800-12,600). However, the mean serum ferritin in cardiac cases was 7645 ± 3404 , while in infection cases was 2314 ± 296 . There was a highly significant difference between both groups with $t = 5.39$, $p < 0.001$, being higher in cardiac cases as seen in Table 2.

Most of the complications and deaths are age related plus iron overload. The mean of age in infection cases was 14.14 ± 2.61 , while in other causes of death was 21.2 ± 2.81 . There was highly significant difference between both groups with $t = 6.04$, $p < 0.002$, being higher in non-infected cases.

Seventy (25%) of the studied 278 cases underwent splenectomy at median age 8 years (range 2.5-15 years). Out of them, 7 died from infection. This represents 10% of the total splenectomized cases. Thus, splenectomy is an additional risk factor.

Figure 3 shows Kaplan-Meier survival curve of patients with TM born in 1975-2000. The median age of death cases was 18 years (range, 10-28 years). It showed that 50% of death cases were at the adolescent and young adults from 16 to 22 years old. A 25% expired below 16 years and 25% died after the age of 22.

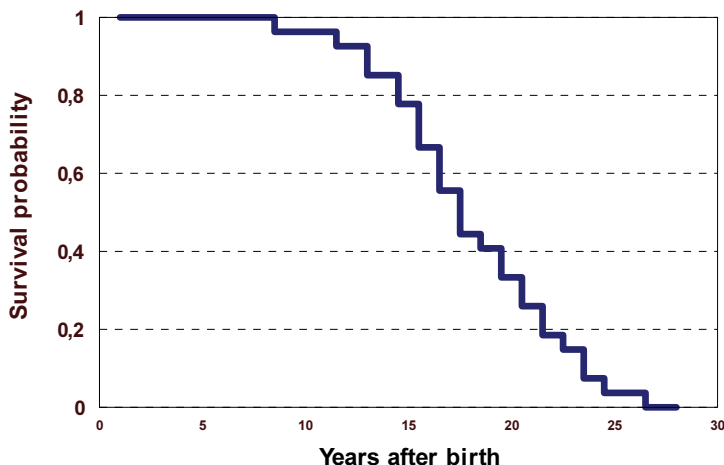


Fig. 3. Kaplan Meier survival curve in the studied 278 patients with thalassemia major treated at KAUH, Jeddah, KSA.

Discussion

Treatment of thalassemia major is complex, expensive and requires a multidisciplinary approach. In this report it defined the current status of disease complication and the causes of death; among 278 patients were treated and followed at KAUH in Jeddah, Saudi Arabia. In spite providing a comprehensive care for this complex group of patients' deaths still occur in young patients.

Iron overload was a major cause of death among our thalassemic patients with the median serum ferritin 4,000 vs. 2,590 for patients who survive. The sixteen-year-old female patient, who died from cardiac, was having the highest level of ferritin 12,600 ng/ml.

Poor compliance with parenteral chelation started at adolescent age as seen in Table 1.

A significant proportion of our patients after age of 12 years; their ferritin measurement exceeded 2,500 ng per milliliter during treatment which is a known risk factor of organ dysfunction^[8]. Most of the complication among thalassemic and organ dysfunction is age-related^[9].

Cardiac constituted the first important cause of deaths in our study which is similar to previous studies^[8,10].

Proper early detection of iron overload on the heart is a crucial management in the thalassemia major. Serum ferritin is a poor indicator of myocardial iron content in early stage of iron overload^[11]. Using a magnetic resonance imaging (MRI) is a reliable and safe non-invasive method for the assessment of early deposition of iron in the heart^[12-15].

Combined chelating therapy in thalassemia major improved the survival^[16-17].

It was observed, an addition risk factor among thalassemic who had splenectomy; 10% of whom had splenectomy died from infection. The ten-year-old female patient who was admitted in septic shock and died in less than 10 hours from admission, was in prophylactic penicillin and up-to-date vaccination, with the median ferritin level of 1,980 mg/ml.

In spite of the complications the overall survival of our thalassemic patients is still good 293 (90.29%).

Conclusion

The prevalence of complication due to iron overload is still high. The survival of patients with thalassemia major in KAUH is good.

Preventive programs of hemoglobinopathies should be implemented as a priority in the Kingdom`.

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دراسة شاملة لمعرفة مضاعفات مرض الثلاسيميا العظمى:
خبرة ١٤ سنة في مستشفى جامعة الملك عبدالعزيز بجدة،
المملكة العربية السعودية

سعاد خليل الجاعوني

قسم أمراض الدم ، كلية الطب ، جامعة الملك عبد العزيز
جدة - المملكة العربية السعودية

المستخلص. مع تقدم وسائل العلاج لمرض الثلاسيميا العظمى
مازال هناك مضاعفات و وفيات لهذا المرض. هذا البحث يقوم
بدراسة مسح شامل لهذه المضاعفات في مستشفى جامعة الملك
عبدالعزيز من ١٩٩٥م حتى ٢٠٠٤م، قمنا بمتابعة ٣٦٠ مريض
بالثلاسيميا العظمى خلال هذه الأعوام، فوجدنا أن السبب الرئيسي
في الوفيات بسبب تراكم الحديد المتزايد في الأعضاء ، ويعتبر
مرض القلب السبب الأول في الوفيات، فننصح بالمتابعة المستمرة
وتوفير العلاج المتكامل لهؤلاء المرضى.