ORIGINAL ARTICLE

Clinical and Haematological Picture of Multi-Transfused Thalassaemia Major Patients at a Center in Pakistan

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ABSTRACT

Objective: To describe the clinical and haematological picture of multiply transfused patients of thalassaemia major at a treatment center in Pakistan.

Study Design: Descriptive cross-sectional.

Place and Duration of Study: The study was conducted at Thalassaemia Treatment Centre Rawalpindi. The study was done between Jan 1994 and May 2017.

Materials and Methods: A total of 383 patients of thalassaemia major (TM) on regular blood transfusions were examined for various clinical and haematological parameters. In addition case records of 101 patients of TM who died during treatment were also studied.

Results: In the 383 patients on treatment 328 (86%) were born to consanguineous parents, 246 (64%) were from lower socio-economic group, 85 (22%) had one or more affected siblings, 145 (38%) had hepatomegaly, 191 (50%) had splenomegaly, 42 (11%) had undergone splenectomy and 187 (49%) had never received iron chelation therapy. Height and weight in the 383 patients on treatment showed marked stunting. Median age of the 383 patients on treatment was 104 months as compared to 119 months in the deceased group of patients (p=0.0263). Pre-transfusion Hb in the alive patients (7.1 g/dL) was higher than in the deceased patients (6.4 g/dL) (p=0.0142). Ferritin level in the patients on treatment (3698 µg/L) was lower than in the deceased patients (4616 µg/L) (p=0.0069). In the 383 patients on treatment 141 (36.8%) were HCV positive.

Conclusion: Majority of the patients at a thalassaemia treatment center are chronically under-transfused and have moderate to severe growth retardation. They get inadequate iron chelation resulting in high mortality before tenth year of life.

Key Words: *Blood Transfusion, Complications, Pakistan, Survival, Thalassemia.*

Introduction

Genetic haemoglobin disorders are the most common single gene disorders in the world. It is estimated that about 250 million people carry the gene for thalassaemia or abnormal haemoglobin.[1] The disease has high prevalence in a broad belt including Mediterranean countries, Middle East, Indian Subcontinent and South East Asia.[2] Successful preventive programs in the developed countries have reduced the new births of thalassaemia major (TM) to almost zero.[3] However, in most developing and under developed countries the picture is very different.[4] Approximately 80% of the new births of children with genetic haemoglobin disorders take place in the under-developed or developing countries that have very limited resources for management and prevention. These have been largely ignored by governments of countries with a high-frequency of these disorders and by the international funding agencies.[5] As the infectious diseases are getting under control the mortality due to genetic diseases like thalassaemia is becoming obvious.[1]

Pakistan has a population of nearly 200 million and approximately 5% of the people carry the gene for β-thalassaemia.[6, 7] It is estimated that each year over 5000 new births of TM take place and the total number of children with TM may be well over 50,000.[8] Most of the children with TM in Pakistan are treated at centers run by Non-Governmental Organizations (NGOs). There are at least 50 NGOs

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that provide blood transfusion services to over 25,000 children with TM. The NGOs work on a charitable basis and are mostly facing paucity of funds. Lack of funds and voluntary blood donations pose great challenge for providing quality treatment to children with TM.[9] There are almost no published data on the outcome of treatment of thalassaemics in Pakistan. This study is the first of its kind that describes the clinical and haematological features of children with TM getting treatment at a center run by a NGO in Pakistan.

Materials and Methods

This descriptive cross-sectional study was done after approval by the ethical review committee of the executive council of the Society. All available children with TM registered at the center between Jan 1994 and May 2017 were examined. The patients of TM registered at the center but not available for examination due to various reasons were excluded. The study variables included age, sex, consanguinity, socio-economic status, other affected siblings, age at diagnosis, age at first transfusion, height, weight, hepato-splenomegaly, splenectomy, pre-transfusion haemoglobin, mean transfusion interval, iron chelation, serum ferritin levels and HCV status. In addition, the case records of children who died while on treatment between Jan 1994 and May 2017 and had adequate documentation were also studied. The deceased patients with incomplete documentation were excluded. The deceased patients were studied for age at death, age at diagnosis, age at first transfusion, mean pre-transfusion haemoglobin, mean transfusion interval, iron chelation, and serum ferritin. The results were analyzed by Stats Direct version 2.5.5 statistical package. Frequency of occurrence of the categorical variables in the alive and the deceased patients was compared by Chi square test and the numerical data were compared by t-test. Survival estimates of the deceased children were made using Kaplan-Meier method.

Results

A total of 383 patients of TM on treatment were examined. Their median age was 104 months that ranged from 6-429 months, the male to female ratio was 1.1:1, 328 (86%) were born to consanguineous parents, 246 (64%) were from lower socio-economic group, 85 (22%) had one or more affected siblings, 145 (38%) had hepatomegaly, 191 (50%) had splenomegaly, 42 (11%) had undergone splenectomy and 187 (49%) had never received iron chelation therapy. Height and weight in the 383 patients on treatment showed marked stunting (Fig 1).

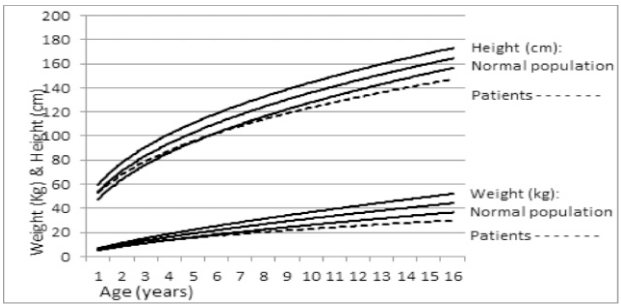

Fig 1: Comparison of Height and Weight of Male Children of TM Aged 1-16 Years and the Normal Population of the Same Age in Pakistan.[10]

It was more marked in the male patients and most of them were below the fifth centile of the Pakistani population.[10] Almost all of the patients were underweight that became more obvious with increasing age (Fig 1). The case records of 101 patients who died during treatment and had adequate documentation were studied. Their median age at the time of death was 119 months that ranged from 6-324 months.

Pre-transfusion Hb in the patients on treatment (7.1 g/dL) was higher than in the deceased patients (6.4 g/dL) (p=0.0142). Average interval between transfusions was four weeks in both of the groups. Ferritin level in the patients on treatment (3698 µg/L) was lower than in the deceased patients (4616 µg/L) (p=0.0069) (Table 1).

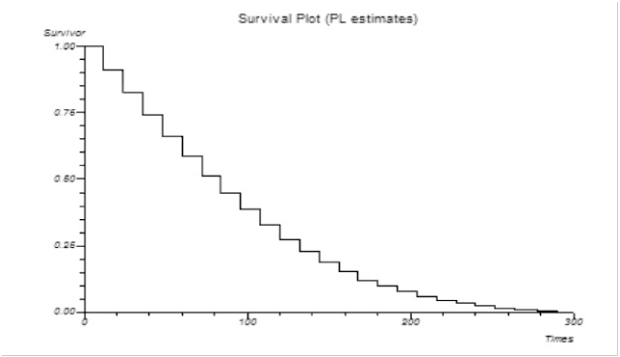

Fig 2: Kaplan-Meier Survival Estimates of 101 Patients of TM Who Died While on Treatment

Out of the 383 TM patients on treatment 141 (36.8%) were HCV positive.

Kaplan-Meier median survival estimate of 101 patients of TM who died while on treatment was 84

months (95% CI 79.21-88.8) (Fig 2). Median survival in the 60 male patients was 72 months (95% CI 65.6-78.4) whereas in the 41 female patients it was 84 months (95% CI 76.2-91.8).

Discussion

Thalassaemia is the commonest single gene disorder in Pakistan.[6] It is estimated that each year over 5000 new children with TM are born and the total number of TM patients may be over 50,000.[8] Treatment of such large numbers of patients is a gigantic task. Unfortunately there are very few public sector institutions that take care of patients with TM. Most of these children are treated at centers run by over 50 NGOs working under the umbrella of Thalassaemia Federation of Pakistan (TFP).[9] In the absence of adequate resources and a mechanism to ensure implementation of treatment guidelines the outcome of treatment at the centers of NGOs is unlikely to improve. There are almost no published data on the outcome of treatment of TM at any of these centers.[9] This study is the first of its kind in Pakistan and it clearly shows a picture of mismanagement. It may not be representative of all thalassaemia treatment centers in Pakistan but it provides a fair idea about the overall scenario.

Table I: Comparison of Age and other Haematological Parameters between Alive and Deceased Patients of TM

Parameter	Alive (n=383)			Deceased (n=101)			P value
	Mean	Median	Range	Mean	Median	Range	
Age at diagnosis (months)	-	8	3-160	-	7	2-180	0.1845
Age at 1st Transfusion (months)	-	6	3-240	-	8	2-180	0.1675
Age at examination/death months) All ages: Male: Female:	- - -	104 105 104	6-429 7-429 6-429	- - -	119 111 132	6-324 10-324 6-286	0.0263 0.2022 0.0269
Pre-transfusion Hb (g/dL)	7.1	-	2.1-12.8	6.4	-	3.0-10.8	0.0142
Transfusions interval (weeks)		4	1-156	-	4	1-16	0.1896
Ferritin (µg/L)	3698	-	840-14900	4616	-	856-14500	0.0069

The Kaplan-Meir estimates showed median survival of 84 months. Survival was longer in the female patients as compared to the male. The longer survival in female patients has also been reported in a previous study.[11] Although it is a cross-sectional study that is not comparable to longitudinal studies on survival but these data are no match for over 68% TM patients surviving at 35 years in an Italian study.[12] High mortality in these patients appears to be due to chronic under transfusion and iron overload due to lack of iron chelation.[13]

Chronic anaemia with pre-transfusion haemoglobin around 7.0 g/dL is clearly reflected by hepato-splenomegaly in nearly half of the patients and stunting of growth in almost all of them. The main reasons for low pre-transfusion haemoglobin include shortage of blood due to insufficient voluntary blood donations and lack of awareness amongst the parents to get timely blood transfusions. The problems can be addressed by creating awareness. It is important for the treating doctors and the parents to understand that maintaining pre-transfusion haemoglobin above 9.0-10.5 g/dL would not only improve the overall health of the child but would also reduce the annual consumption of blood. When a child with TM remains chronically under transfused erythropoietin is constantly released and stimulates bone marrow. The resulting marrow expansion and hepato-splenomegaly cause haemodilution and worsening of anaemia. This vicious circle can be broken only by correcting anaemia through blood transfusions.[13] The treating doctors should make an extra effort to guide the parents about benefits of high transfusion regimens. The shortage of blood can be met by public awareness through mass media about voluntary blood donations.

Iron overload is an invariable complication of TM. It is mostly caused by regular blood transfusions. The extra iron is carried in plasma through transferrin and when the latter is fully saturated iron travels as non-transferrin bound iron (NTBI).[14] NTBI is preferentially taken up by myocardium, endocrine glands and hepatocytes and is responsible for growth failure, hypogonadism, hypothyroidism and diabetes etc. Myocardial haemosiderosis is another life threatening complication of iron over load that causes conduction defects and cardiac failure.[13] The age at which iron chelation is started is the key factor because starting it late in life is much less effective.[12]

Cardiac complications resulting from iron deposition are the commonest cause of death in TM.[12] The peak mortality observed around ten years of age in this study also appears to be related to cardiac haemosiderosis. Stature of the vast majority of

patients in this study was below 5th centile of the Pakistani population.[10] Growth retardation is common in TM after the first decade of life. It is mostly because of chronic anaemias, endocrinopathy due to iron overload, malnutrition, zinc deficiency, chronic liver disease and psychological stress.[13]A previous study on endocrine abnormalities in 131 children from the same center showed growth hormone deficiency in 30%, hypoparathyroidism in 17.5%, hypothyroidism in 8%, diabetes mellitus in 1.5% and impaired fasting glucose metabolism in 4% of TM patients.[15] In this study growth retardation in the male patients became obvious after the fifth year of life whereas in female patients it was less significant. In the female patients it usually appears after the tenth year of life.[16] Growth retardation at a very early stage appears to be related to chronic anaemia, malnutrition and marked iron overload.

Nearly half of the patients in this study had never used iron chelation and even those who were using it were getting it infrequently and at suboptimal doses. This is also reflected by grossly elevated serum ferritin levels. The high cost and lack of awareness are the two main limiting factors in the wider use of iron chelation. Nearly 2/3rd of the patients in this study are from the lower socio-economic group and are unable to bear the high cost of iron chelation. Low-cost oral iron chelators are an urgent requirement and efforts should be made to facilitate their local production.

Hepatitis C virus (HCV) infection is another problem area in the management of TM in Pakistan. Nearly 40% of the patients in this study were positive for HCV. Previous studies have also shown that 40-50% of the TM patients are HCV positive.[17,18] Poor screening facilities at many centers are the major cause of high HCV prevalence in TM. Many patients keep visiting different treatment centers in search of blood. Since the screening facilities at all centers are not uniform the patients can easily get HCV infection by one wrong transfusion. The HCV point of care testing devices are known to give false negative results due to their low sensitivity.[19,20] These devices are in common use by majority of the blood banks in Pakistan and are partially responsible for the high prevalence of HCV in multiply transfused patients of TM in Pakistan.

Voluntary carrier screening and prenatal diagnosis of thalassaemia are available in Pakistan since 1994.[21] It is unfortunate that most of the children with TM in this study and elsewhere in Pakistan were born during the period when prenatal diagnosis was available. This study also showed that 22% of the TM patients had at least one affected sibling. Lack of awareness amongst the doctors and the parents and high cost of testing are the two major limiting factors in the use of prenatal diagnosis in Pakistan.[22]

Consanguinity, also seen in this study, is an important contributing factor in causation of recessive genetic disorders in Pakistan.[23] The best way to tackle this sensitive issue would be to offer premarital carrier screening in the close family setting or to offer prenatal diagnosis where marriage between two carriers is unavoidable.[6]

Conclusion

Majority of the patients at a thalassaemia treatment center in Pakistan are chronically under-transfused and have moderate to severe iron overload. This results in severe growth retardation and high mortality around ten years of age. The outcome of treatment can be improved by creating awareness and providing adequate amount of blood and iron chelating drugs.

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