ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI ARTICLE International Journal of Hematology and Oncology

Common Complications in Beta-Thalassemia Patients

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ABSTRACT

Even the life span has prolonged for the last 40 years, increase in frequently seen complications with increasing age negatively affect the life quality of thalassemia patients. In our study, complications encountered in 67 ß-thalassemia patients who were followed-up at our hospital between 1 January 2004 and 31 May 2009 were retrospectively analyzed. Fifty-six patients were followed up with diagnosis of thalassemia major and 11 with thalassemia intermedia. Totally, 56.7% of patients were male and 43.3% were female. Ages varied between 2-20 years with the mean age of 10.3±4.8 years. Mean ferritin level was 2212±1370 ng/mL (41-6263 ng/mL) for 4.5 years. Complications were increased with increasing age. Complication rates were significantly higher among thalassemia major patients compared to thalassemia intermedia patients. There was no statistically significant relationship between complications and mean ferritin levels. The most common complications were endocrine complications (38.8%). Cardiac complications developed in 22.4% of the patients; gastroenterological complications in 19.4%; allergic complications in 9%; infectious complications in 1.5%; and thrombosis was detected in 1.5%. The endocrine complications were osteoporosis, growth retardation, developmental delay, short stature, hypothyroidism, delayed puberty, hypogonadism, and diabetes mellitus. The cardiac complications were left ventricular wall hypertrophy, diastolic dysfunction, systolic dysfunction, heart failure, pericardial effusion, dilated cardiomyopathy, left ventricular dilatation, left atrial dilatation, and fatal arrhythmias. Mortality occurred in one (1.5%) out of 67 ß-thalassemia patient due to dilated cardiomyopathy and fatal arrhythmia.

Keywords: Thalassemia major, Thalassemia intermedia, Complications

ÖZET

Beta Talasemili Hastalarda Sık Görülen Komplikasyonlar

Talasemi hastalarının son 40 yıl içerisinde yaşam sürelerinde uzama olmakla birlikte yaş arttıkça görülen komplikasyonlar hastaların yaşam kalitelerini olumsuz yönde etkilemektedir. Çalışmamızda 1 Ocak 2004-31 Mayıs 2009 tarihleri arasında hastanemizde takipli 67 ß-talasemi hastasında görülen komplikasyonlar retrospektif olarak incelenmiştir. Çalışmaya dahil edilen hastaların 56'sı talasemi majör, 11'i talasemi intermedia tanısıyla takip edilmektedir. Olguların %56.7'si erkek, %43.3'ü kız idi. Yaşları 2-20 yıl arasında olup, yaş ortalamaları 10.3±4.8 yıl olarak hesaplandı. Hastaların 4.5 yıl boyunca bakılan ortalama ferritin düzeyleri 2212±1370 ng/mL (41-6263 ng/mL) olarak bulundu. Hastaların komplikasyonlarında yaşla birlikte artış olduğu saptandı. Komplikasyonlar talasemi majörlü hastalarda talasemi intermedialı hastalara göre istatistiksel olarak anlamlı derecede daha sık görüldü. Ortalama ferritin değeri ile komplikasyon gelişme sıklığı arasında istatistiksel olarak anlamlı bir ilişki bulunmadı. Hastalarımızda en sık rastlanan komplikasyonlar %38.8 oranı ile endokrin komplikasyonlardı. Olguların %22.4'ünde kardiyak, %19.4'ünde gastroenterolojik, %9'unda allerjik, %1.5'inde enfeksiyöz komplikasyonlar ve %1.5'inde tromboz saptandı. Endokrin komplikasyonlar osteoporoz, büyüme-gelişme geriliği, boy kısalığı, hipotiroidi, puberte gecikmesi, hipogonadizm ve diyabetes mellitus idi. Kardiyak komplikasyonlar olarak sol ventrikül duvar kalınlaşması, diyastolik disfonksiyon, sistolik disfonksiyon, kalp yetmezliği, perikardiyal efüzyon, dilate kardiyomiyopati, sol ventrikül genişlemesi, sol atrium genişlemesi ve fatal aritmi görüldü. Çalışma süresi içerisinde 67 ß-talasemi hastasından biri (%1.5) fatal aritmi ve kardiyomiyopati nedeni ile kaybedildi.

Anahtar Kelimeler: Talasemi majör, Talasemi intermedia, Komplikasyonlar

INTRODUCTION

Thalassemias are hereditary hemolytic anemias with autosomal recessive inheritance characterized by inability to produce one or more globin chains forming hemoglobin molecule.[1] It is seen more frequently than expected in our country due to high consanguineous marriage and birth rates. While incidence of ß-thalassemia trait is 2.1% in our country, it may elevate up to 13.6% in Mediterranean and Aegean regions. There are approximately 1.300.000 carriers and 4000 patients in our country.[2]

Regular blood transfusion and adequate iron chelation therapy are important factors for treatment and follow up of thalassemia patients. Currently, the most common causes of death in these patients are transfusion-related hemosiderosis-induced heart failure and fatal arrhythmias. Osteoporosis, bone pain and bone changes, bile stone formation, increased risk of viral hepatitis, cirrhosis, delayed puberty, growth retardation, developmental delay, diabetes mellitus, and hypothyroidism are the other common complications.[3]

In this study, demographic features, clinical and laboratory findings, and complications of ß-thalassemia patients were evaluated retrospectively.

PATIENTS AND METHODS

In our study, data of 67 ß-thalassemia patients followed up at Department of Pediatric Hematology, Dr. Sami Ulus Maternity and Children's Research and Training Hospital, Ankara, Turkey, between 1 January 2004 and 31 May 2009, were retrospectively evaluated. Fifty-six patients were followed up with diagnosis of thalassemia major and 11 with thalassemia intermedia. Thalassemia major patients is treated with regular blood transfusions to maintain pretransfusion hemoglobin (Hb) levels ≥ 9-10 g/dL.Thalassemia intermedia patients received erythrocyte transfusion when hemoglobin level was below 7 g/dL. Iron chelation therapy was started for patients whose ferritin values were above 1000 ng/mL and whose age was appropriate for chelation therapy. Desferrioxamine, deferiprone, deferasirox or desferrioxamine and deferipone combination therapies were used as iron chelation therapy. Thalassemia major cases whose erythrocyte consumption exceeded 200-250 mL/kg/year and thalassemia intermedia cases who developed hypersplenism or who need increased transfusion underwent splenectomy. Hematopoietic stem cell transplantation was performed for 10 patients in different institutions. Three patients did not come for follow up visits after 1.5 year follow up duration.

Clinical histories, physical examinations, laboratory values [hemoglobin, platelet count, fasting plasma glucose, renal function tests, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, calcium, phosphorus, alkaline phosphatase levels, serology for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, ferritin levels, follicle stimulating hormone, luteinizing hormone, estradiol, testosterone, vitamin D, parathormone levels, thyroid function tests (thyroid stimulating hormone, T3, T4), insulin level] and radiological findings (abdominal and thyroid ultrasonography, bone x rays, T2w magnetic resonance imaging) were evaluated from the patient files. Electrocardiography (ECG), echocardiography (ECHO), and bone mineral densitometry (BMD) results were also evaluated for development of complications.

Data were analyzed using SPSS for Windows 16.0 program. Categorical variables were given as number and percent, numerical variables were reported as mean ± standard deviation and median. The difference between groups in terms of categorical variables was evaluated by using qui-square test. Level of significance was taken as $p< 0.05$.

RESULTS

A total of 67 ß-thalassemia patients including 38 (56.7%) boys and 29 (43.3%) girls with the age range of 2-20 years were evaluated retrospectively. Fifty-six of the patients were followed up with diagnoses of thalassemia major and 11 with thalassemia intermedia. Of thalassemia major patients, 28 (50%) were boys and 28 (50%) were girls. Of thalassemia intermedia patients, 10 (90.9%) were boys and 1 (9.1%) was a girl. The mean age of the patients was 10.3±4.8 years (range: 2-20 years).

Parenteral desferrioxamine, oral deferiprone or deferasirox were used for iron chelation therapy. Type of chelation therapy is given in Table 1.

Table 1. Type of chelation therapy for thalassemia major patients

Chelator	n	%
Desferrioxamine+Deferiprone	23	41,1
Deferasirox	18	32,1
Desferrioxamine	15	26,8
Total	56	100

Thirteen patients with thalassemia major and 4 patients with thalassemia intermedia underwent splenectomy. Ten (14.9%) patients underwent hematopoietic stem cell transplantation in different institutions.

Mean ferritin level was 2212±1370 ng/mL (41-6263 ng/mL) for 4.5 years. Mean ferritin level was 2515±1221 ng/mL (797-6263) for thalassemia major patients and 667±1022 ng/mL (41-3697) for thalassemia intermedia patients. Mean ferritin values were <2500 ng/mL in 65.7% of patients and > 2500 ng/mL in 34.3% of patients.

At least one complication was detected in 64.2% (n: 43) of the patients and complications involving more than one system was detected in 26.8% of the patients. A statistically significant difference was not found between gender and complications (p> 0.05).

Complications developed in 39 of 56 (69.6%) thalassemia major patients and in 4 of 11 (36.4%) thalassemia intermedia patients. Complication rates were significantly higher in thalassemia major patients compared to thalassemia intermedia patients (p< 0.05). When the rate of complications was compared between the patients with age range of 1-10 years and 10-20 years; the rate of complications was increased in older patients (p< 0.05).

Mean ferritin levels of the patients in the first and second decade were compared. Among all _-thalassemia patients; 75% of the patients in the first decade and 57.1% of the patients in second decade had mean ferritin levels <2500 ng/mL. The mean ferritin values were higher with increasing age, but was not statistically significant (p> 0.05).

Complications were compared with mean ferritin levels. While complications developed in 61.4% of the patients whose mean ferritin level was <2500 ng/ml, it developed in 69.6% of the patients whose mean ferritin level was >2500 ng/ml, whereas there was no statistically significant relationship between mean ferritin levels and complications (p> 0.05).

The most common complications were endocrine complications (38.8%). Cardiac, gastroenterological, allergic, and infectious complications developed in 22.4%, 19.4%, 9% and 1.5% of patients respectively and thrombosis was detected in 1.5% of patients.

Of the patients, 38.8% have been followed up for one endocrine complication and 14.9% have been followed up for more than one endocrine complication. The most common endocrine complications were osteoporosis (20.9%) and growth-developmental retardation (19.4%) (Table 2).

Osteoporosis-induced fracture was detected in one case. When relationship between endocrine complications and mean ferritin values was evaluated, complications were detected in 34.1% of the patients with ferritin levels < 2500 ng/mL, and in 47.8% of the patients with mean ferritin levels >2500 ng/mL. However, there was no statistically significant relationship between mean ferritin levels and endocrine complications (p> 0.05).

The second leading complications were cardiac complications (22.4%). Cardiac iron load was studied with T2w MRI in 12 out of 56 thalassemia major patients. Severe involvement (<8 msec) was detected in one patient, moderate involvement (8-14 msec) was detected in 2 patients and mild involvement (14-20 msec) was detected in 5 patients. Four patients were normal (>20 msec). Cardiac complications are shown in Table 2. There was no statistically significant relationship between mean ferritin levels and cardiac complications (p> 0.05).

Gastroenterological complications were seen in 19.4% of the patients. Patients were evaluated in terms of constant transaminase elevation, bile stone formation and hepatic failure. Constant transminase elevation was detected in 17.9% of the patients, temporary transaminase elevation was detected in 50.7%, and bile stone was detected in 1.5% of the patients. No patients developed hepatic failure. Transaminase elevation was statistically significant in the patients whose mean ferritin level was >2500 ng/mL (p< 0.05).

Table 2. Distribution of complications

Complications		Patient group	
		n	%
Cardiac (22.4%)	Increase in left ventricle wall thickness	7	10.4
	Diastolic dysfunction	5	7.5
	Systolic dysfunction (EF<%55)	4	6.0
	Heart failure	3	4.5
	Pericardial effusion	2	3.0
	Dilated cardiomyopathy	1	1.5
	Left ventricle enlargement	1	1.5
	Left atrium enlargement	1	1.5
Endocrine (38.8%)	Osteoporosis	14	20.9
	Growth retardation-short stature	13	19.4
	Hypothyroidism	6	9.0
	Delayed puberty-hypogonadism	6	9.0
	Diabetes mellitus	1	1.5
Allergic (9.0%)	Transfusion-related	3	4.5
	Chelation-related	3	4.5
Gastroenterological (19.4%)	Constantly elevated transaminases	12	17.9
	Bile stone	1	1.5
Infectious (1.5%)	Chronic Hepatitis B	1	1.5
Others (1.5%)	Thrombosis-hemiplegia	1	1.5

HBV infection was detected in 1.5% of all patients. There were no patients positive for HCV or HIV. A rare complication of thrombosis-related cerebrovascular event and left hemiplegia was observed in one patient with ß-thalassemia major. This patient had both protein C and S deficiency.

Three patients developed transfusion-related allergic complications and 3 had deferasirox-induced allergic rash.

Cardiac complication-induced mortality occurred in one (1.5%) patient. He was 14-year-old when he died. Dilated cardiomyopathy and fatal arrhythmia were the causes of his death.

DISCUSSION

While untreated, thalassemia major patients die during the first few years of life; patients may survive until 4th-5th decades through regular transfusion programs, appropriate chelation therapy, and effective treatment of complications. Transfusion treatment is life-saving for the patients who are followed up with ß-thalassemia major. However, hemosiderosis and transfusion-related infections emerge as the main causes of mortality and morbidity.[4]

In thalassemic patients, complications usually begin to appear after 1st decade and increase with age.[4] In this study, complications were more frequent among thalassemia major patients than thalassemia intermedia patients and significantly increased with age ($p< 0.05$).

Since ferritin is an iron indicator with low specifity and sensitivity; a significant relationship could not be found between complications and mean ferritin levels. The most accurate indicator of iron deposition is tissue iron level. However detection of tissue iron is an invasive procedure and could not be applied to our patients. MRI is a non-invasive method providing the most accurate results for measuring parenchymal iron load.[5]

In our study, the most common complications were endocrine complications (38.8%). Osteoporosis is a common problem among thalassemia patients. Hypogonadism and hypoparathyroidism are commonly seen in these patients besides elevated iron load, cortical thinning resulting from bone marrow expansion, negative effects of chelator agents on calcium, phosphorus absorption compose osteoporosis in thalassemias.[6] Osteoporosis was detected in 20.9% of our patients. Osteopenia/osteoporosis was found in 56-96% of thalassemia patients in studies conducted with large patient series.[7-9] This high ratio indicates the importance of close follow up of the patients in terms of osteoporosis and appropriate treatment should be given in early period.

There was growth retardation in 19.4% of the patients. In a similar study by Cario et al., they reported growth retardation in one third of 203 patients with mean age of 13.8 years (1-37.5 years) and in more than half of the patients older than 15 years.[10] Causes of growth retardation that usually becomes remarkable in puberty are chronic anemia-related chronic hypoxemia, increased calorie need due to increased erythropoiesis, growth hormone deficiency that may develop as a result of toxicity on hypothalamo-hypophysial level caused by increased iron load, hypothyroidism, inability to make the growing spurt because of delayed puberty and hypogonadism and psychosocial factors.[11-14]

Hypothyroidism that usually appears in the second decade in thalassemia patients is seen in the ratio of 6-24%.[15,16] In our study, hypothyroidism was detected in 9% of the patients and this result was attributed to the fact that most of our patients are in the first decade.

Delayed puberty is defined as puberty signs not appearing until 13.5 years for girls and 14 years for boys. In our study, delayed puberty and hypogonadism were detected in 9% of thalassemia patients. These patients were between the ages of 14 and 17.5 years and 50% were boys. In a study conducted with 250 thalassemia major patients with the age range of 12-16 years, 38% of thalassemic girls and 67% of thalassemic boys did not have puberty signs.[17] In another study, hypogonadism was detected in 54.3% of girls >15 years and in 63.6% of boys >17 years.[18]

A statistically significant relationship could not be found between endocrine complications and mean ferritin levels in our study ($p > 0.05$). These types of complications can be seen more frequently after 1st decade of life and mean age of our patients was 10.3 years. In a study of Borgna-Pignatti et al., hypogonadism was less detected in the patients whose ferritin was <2500 ng/mL.[16] In another study of the same authors, heart failure and hypogonadism were decreased and expected life span was increased in patients with low ferritin levels.[7]

In thalassemic patients, cardiac complications caused by excessive iron load are pericarditis, arrhythmias, and myocardial insufficiency.[19] In our study, the second leading complications were cardiac complications with a ratio of 22.4%. In a study evaluating 203 ß-thalassemia patients, cardiac diseases were reported in 13% of the patients.[10] In a similar study by Atiq conducted in 75 ß-thalassemia major patients, systolic dysfunction was detected in 22.6% of patients (EF<55%), diastolic dysfunction in 29.3%, and pericardial effusion in 16%.[20] While mean age of the patients was 13,8±5,5 years in that study, mean age of our patients was 10.3 ±4.8 years and the probable reason of less complications is the younger age in our study. Similar to our study, Kosaryan et al. reported the rate of diastolic dysfunction was 9%; systolic dysfunction, 5%; and severe cardiomyopathy, 5.7%.[21] In a study investigating thalassemia intermedia patients, heart failure was 5.4%; aortic insufficiency, 15.4%; and, mitral valve insufficiency, 47.2%.[22]

Cardiac complications were compared with mean ferritin values. Although cardiac complications were seen more frequently in the patients whose mean ferritin levels were >2500 ng/mL, this was not statistically significant ($p > 0.05$). In a study, life span without complications was longer in the patients whose ferritin levels were <1500 ng/mL and shorter in the ones with ferritin levels >3000 ng/mL. In

the same study, 55 deaths were reported and 60% of them were detected to be caused by heart failure.[23] In the study of Ladis et al., survival at 40 years declined up to 28.9% in the patients whose serum ferritin levels were >4000 μg/L. In the same study, 115 deaths occurred and the leading cause of death was hemosiderosis (76.5%) with 71.3% of cardiac diseases followed by sepsis (7.8%) and AIDS (6.1%).[24] Non-invasive techniques measuring myocardial iron deposition may aid for determining cardiac iron deposition. Cardiac T2w MRI is a standardized and proven method for determining cardiac iron intensity with gradient echo imaging. While T2w MRI >20 msec defines normal iron load in the heart, 14-20 msec corresponds to mild, 8-14 msec corresponds to moderate, and <8 msec corresponds to severe iron load.[25] Besides serum ferritin levels, monitoring cardiac iron intensity with T2w MRI once a year (maximum twice) after 10 years of age may provide advantages for management of iron chelation therapy, keeping iron load in safe and, optimum levels.

Free radicals formed by accumulated iron in the body, especially in the liver because of frequent transfusions lead to apoptosis and hepatic fibrosis. However, routine application of liver biopsy is difficult and monitorization of serum ferritin levels is easier and more practical.[26] Liver MRI is an effective technique used for indication of hepatic iron load.[27]

Thrombosis-related cerebrovascular event and left hemiplegia was detected at 1.5%. Turkish Thalassemia Study Group reported that thromboembolism incidence was 3.27% in thalassemia patients in Turkey.[28] In the study of Borgna-Pignatti et al. including 9 distinct thalassemia institutions, they reported thromboembolism episodes as 3.95% in thalassemia major patients and 9.61% in thalassemia intermedia patients.[29]

In our study, one patient died from fatal arrhythmia and cardiomyopathy at the course of the study. Of the deaths, 70% are related to cardiac decompensation resulted from iron overload.[30] Cardiac-disease related death was between 38.0-71.3% in ß-thalassemia patients.[16,24,31]

In conclusion, complications have significantly increased with prolonged life span in ß-thalassemia patients in recent years. Especially organ damage caused by iron overload in the heart and endocrin organs severely impairs quality of life. Currently, the most common cause of death among thalassemia patients is hemosiderosis-related heart failure and fatal arrhythmias. Non-invasive imaging techniques have gained importance as serum ferritin levels alone are not sufficient for monitoring body iron load. It is obvious that following hepatic iron overload with R2 MR once or twice a year and cardiac iron overload with T2w MRI once or twice a year would provide advantages for management of iron chelation therapy, keeping iron levels in safe, optimum levels, and preventing complications.

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