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Evaluation of the level of Growth Hormone Secretion in Patients with Thalassemia Major

Research Article

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Abstract

Introduction: Thalassemia Major Illness is mainly created as a progressive hemolytic anemia within the next six months of life after birth. Therefore, the aim of the present study is to evaluate the level of growth hormone secretion in patients with thalassemia major. Methods: The present research is a descriptive-analytic study. 97 patients with major thalassemia were selected. All patients test files were examined. Demographic information of each patient was gathered using a questionnaire. Fasting blood samples were taken from patients and the level of growth hormone was measured. Results: The participants of the study were 95 patients (48 males and 47 females). The youngest patient was a seven-month girl and the oldest one was a 27- year- old girl. The average age of patients was 13.48 years old. All patients were under transfusion. After stimulation with clonidine, 45.26% and 54.74% of patients did not have a significant increase in growth hormone and growth hormone secretion, respectively. Conclusion: The study indicates that there is a significant relationship between Failure to thrive (FTT) and thalassemia patients. And the highest degree of FTT is at the age of over 14 years and poor control of plasma ferritin level plays an important role in delayed puberty. Therefore, in order to prevent FTT, patients are required to be regularly examined in terms of growth rate and the factors involved in FTT should be determined and appropriate preventive measures should be taken.

Keywords: Beta Thalassemia Major (BTM), growth hormone, Clonidine.

Introduction

Today, chronic diseases are the major cause of health problems in developed countries. Such diseases occur in all age groups, social and economic classes, and different cultures. It is anticipated that by 2050, 167 million people will be affected by chronic disease. According to information obtained from the United States National Research Association, 15 -18 percent of children and adolescents suffer from chronic disease, which has nearly doubled over the last two decades (1). β thalassemia major is one of the chronic diseases that threaten the children's health. The World Health Organization has identified thalassemia as the most commonly diagnosed chronic genetic disorder in 60 countries, affecting about 100,000 children a year (2). Thalassemia is a heterogeneous group of Hereditary Hemolytic Anemias which are in common with reducing the amount of synthesis of one or more globin polypeptides. Due to the type of trapped chain in thalassemia patients, the disease can be divided into two groups: α-thalassemia and β-thalassemia syndromes (3, 4). There are more than two million beta thalassemia carriers and more than 15,000 people live with β thalassemia major in Iran (6). The outbreak of beta-carriers in Iran, in the Northern provinces of Iran (Golestan and Mazandaran provinces) and southern coasts (Hormozgan and Khuzestan provinces) is about 4% (7) , it is more common and is evident more or less in other areas. (8). Beta-thalassemia syndromes are classified into four subsets in terms of the severity of clinical symptoms: silent carriers, β thalassemia minor, intermedia thalassemia, and thalassemia major (9, 10). Beta-thalassemia major is one of the diseases in which normal human development is impaired due to complications from the disease (11). The growth retardation in beta-thalassemia patients depends on several factors that can be attributed to chronic anemia, folic acid deficiency, overactive spleen, endocrine disruption, zinc deficiency and Desferal poisoning [12]. Thalassemia treatment is performed in patients with β thalassemia major via bone marrow transplantation and blood transfusion (13, 14). Bone marrow transplant is a certain cure for thalassemia major (15, 16). The most important part of patients' treatment with thalassemia major is a blood transfusion, which includes various goals (17). Blood transfusions in such patients are based on the Thalassemia International Federation (TIF) protocol. Blood transfusion treatment in thalassemia patients leads to removing hypoxia pressure and severity of erythropoiesis and also reduces the absorption of iron from the digestive system. On the other hand, it increases the iron overload due to blood transfusion in these patients (18). Despite clinical benefits of repeated blood transfusions in such patients, it can lead to an inevitable Hemosiderosis in the long run and cause tissue impairment in the form of liver disorders, heart failure, growth disorders, hypogonadism, hypothyroidism and parathyroidism, and Diabetes (19, 20). To prevent such complications, extra iron should be removed by iron removal (usually done with

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deferoxamine), while endocrine disorders are still seen in these patients, as they get older some of these complications increase (21, 22). Growth disorder is a clear phenomenon in patients with thalassemia, which is often associated with diminished growth in moderate retardation. Delay in growth and short stature is observed in more than 40% of thalassemia patients. Generally, the decline in the rate of growth begins at the age of 10-11 and then continues, so that the height of such children is less than the average height of parents (7, 15). Short stature in thalassemia patients has been abundant in spite of regular blood transfusions and chelator therapy (iron reducing agents). Several factors such as abnormal gonadotropin secretion during puberty, poor acceptance of iron regimen (iron accumulation), inappropriate diet, liver disease, zinc deficiency, GH-IGF1 axis disorders and bone dysplasia after taking deferoxamine (toxic effect) are effective in Short stature (23,24). The cause of growth impairment in children is due to the low activity of somatomedin, which is a kind of protein that the growth hormone induces by its effect. Because the growth hormone was induced by cells in vitro, there was no significant change in their growth. Since somatomedin is made by the liver, Liver hemosiderosis is responsible for premature growth impairment (25). Therefore, due to the large number of thalassemia patients and considering growth hormone disorders which are the most common in thalassemic patients, the aim of the present study is to investigate growth hormone disorders in thalassemia patients.

Materials and Methods

The cross-sectional descriptive-analytic study was conducted in thalassemia center in Qazvin-Iran. The population of the present study included 97 patients with β-thalassemia major (previously diagnosed and confirmed) covered by Qazvin-Iran thalassemia center (located in Quds Hospital). There existed all the patients' folder in Quds Thalassemia Center. First, demographic information for each patient was gathered, then, a fasting blood sample was taken. After, they were given clonidine based on their weight, (0.005 mg / kg) to stimulate growth hormone (mg / kg). After 120-190 min (peak growth hormone secretion), the next sample was taken to determine the stimulated growth hormone level. Then, Samples were transferred to the Quds hospital laboratory. After centrifugation and separation of the serum from the clot, the samples were transferred to the hormone section of the Bu-Ali Sina laboratory in Qazvin-Iran. Freeze samples were kept in a lab and melted for testing once. Inappropriate, suspected or hemolytic samples (2 samples) were excluded in the study. Experiments were carried out using Immuno tech kit method with high precision. The study is based on IRMA (Immuno Radiometric Assay) method which is one of the labeled radioisotope methods with high accuracy. Then, the results and the information in the patients' questionnaire (such as age, sex, time of transfusion, number of transfusion per month) and the level of ferritin in patients were analyzed.

Results

The following results have been obtained in 95 patients with β thalassemia major in thalassemia department of Quds Hospital. A total of 95 patients with beta-thalassemia major were 48 males (52/50%) and 47 females (48/49%), respectively. 26.5% were at the age of under 5 years old, 24.21% at the age of 9-5 years, 26.31% at the age of 10-14 years, 27.36% at the age of 19-15 Year, and 16.66% at the age of over 20 years (Table 1). The highest number of patients belonged to 26 persons at the age of 19 -15 years old (27.36%) and the lowest number of patients were 5 persons (5. 26%) at the age of less than 5 years.

Table 1: Relative Frequency Distribution of patients with Thalassemia major According to Age

Age	Percent	Number
5>	5.26	5
5-9	24.21	23
10-14	26.31	25
15-19	27.36	26
20<	16.86	16

The youngest patient was a 7-month-year-old baby girl and the oldest patient was a 27- year- old girl. The average age of patients was 13.48 years. The average age of onset of blood transfusion was 13 months years of age. The earliest onset of blood transfusion was from 3 months and the shortest time was 10 years old. A total 95 patients, one person once 40 days, 45 people once per month, 37 persons twice every month, 11 persons once 20 days, and one person once 10 days received blood. A total of patients, 82.75% consumed Desferal irregularly and 17.25% consumed Desferal regularly (Table 2).

Table 2: Relative Frequency Distribution of patients with Thalassemia Major According to Desferal Consumption

Desferal Consumption	Percent
Regular Consumption	17.25
Irregular Consumption	82.75
Total	100

80 patients have had ferritin measurements in which 2 patients (2. 5%) had ferritin below 1000 ng/dl, 19 persons (23.75%) at the range of 1000-1000 ng/dl, 28 persons (35%) at the range of 3000-2000 ng/dl ,and 31persons (38.75%) greater than 3,000 ng/dl. The highest (38.75%) and the lowest (2.5%) number of patients with ferritin level were above 3000 ng/dl and below 1000 ng/dl, respectively. The lowest amount of ferritin was 600 ng/dl and the highest one was 8350 ng/dl. The following results were obtained in evaluating the response rate of the growth hormone secretion to clonidine stimulation: 42 patients (45.26%) had an increase of more than 5-7 ng/dl in response to stimulation with clonidine which indicates an appropriate response. 52 patients (54.74%) had a normal

increase in response to stimulation with clonidine which indicates the growth hormone secretion disorder. Out of 52 patients with growth hormone disorder, 4 patients (7.69%) were at the age of under 5 years old, 14 (26.99%) were at the age of 5-9 years, 16 (30.76%) were at the age of 10-14 years, 13 (25%) were at the age of 15-19 years, and 5 patients (9.63%) were at the age of over 20 years old.

Table 3: Distribution of patients with growth hormone secretion disorder

	Age	Number (percent)
52 patients	<5	4 (7.69%)
	5-9	14 (26.99%)
	10-14	16 (30.76%)
	15-19	13 (25%)
	>20	5 (9.63%)

Discussion

Despite all the advances have been made in the treatment of patients with β thalassemia major, FTT is still a major problem in these patients (26). Thalassemia major illness is a severe form of β thalassemia which causes ineffective bone marrow activity, hemolytic, and severe and progressive anemia and patients usually will be dependent on blood transfusions in the first year of life (27). According to the various studies conducted in endocrine changes in patients with thalassemia major, different hormonal disorders have been observed which are due to iron overload disposition from transfusion. Growth hormone secretion disorders are one of the most common endocrine disrupters in such patients (28, 29). In this study, 54.74% of the patients with thalassemia major had growth hormone secretion disorder and 45.26% of the growth hormone secretion was normal. In a study conducted at Shahid Beheshti University of Medical Sciences in Iran, it has also been reported that there is a low level of growth hormone secretion in a number of patients with thalassemia major, while some have no growth hormone secretion disorder (30). A research which was conducted Khalili et al. indicated that more than 90% of patients with β-thalassemia major had a growth rate of less than 50% (31). In related studies, it is reported that short stature was a common complication in such patients (32). Shiva et al. found out more than 50% of the patients over 10 years of age had short stature, and only 10% of the patients under the age of 10 were short stature (33). Although the growth retardation in patients with β-thalassemic began in the first decade, it usually drops at the age of 9-10 years old using today's treatments and a significant percentage of these patients ultimately become short stature (34). In the present study, the most common age group of people with growth hormone secretion disorder is 10-14 years old (puberty). According to the available sources, most of the iron overloads including progressive cardiac, liver and endocrine is created in the second decade of life. In addition, it was observed that the more the serum ferritin levels increase, the more the number of patients with growth hormone secretion disorder increase (in particular, levels> 3000 ng/dl). According to the available sources, iron overload with high levels of ferritin is the main cause of endocrine disorder function including pituitary and reduction of growth hormone (28). In a study done by Gulati et al (2000) 84 patients with thalassemia major were observed in which 51% of the patients were with GH deficiency, 10 out of 11 adults were with hypogonadism, and out of 54 children who were under dynamic testing before puberty,18 patients showed endocrine disorder and short-term growth (8). According to the present research and previous studies, growth defects in patients with thalassemia depend on several factors. One of the most important negative factors are the toxic and harmful effects of Deferoxamine and Desferal which are mainly due to the increased iron levels.

Conclusion

The results of the present study indicate that patients with β-thalassemia major have been at increased risk of growth disorders and it increases with age. Therefore, it is necessary to be monitored regularly at the beginning of life in terms of growth condition, and the factors involved in their developmental disorder should be identified in time and appropriate preventive measures are required to be taken.

Conflict of interest

None

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