

Original Article

The Study of Growth in Thalassemic Patients and its Correlation with Serum Ferritin Level

Hashemi A MD¹, Ghilian R MD², Golestan M MD³, Akhavan Ghalibaf M MD⁴, Zare Z MD⁵, Dehghani MA MSc⁶

- 1- Department of Pediatrics, Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 2- Internal Medicine. Hematology oncology and Genetics Research Center Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 3- Department of Pediatrics, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 4- Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 5- General Practitioner.
- 6- Master of Nursing, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.

Received: 25 July 2011
Accepted: 22 November 2011

Abstract

Background

Beta-thalassemia is a common hereditary hemoglobinopathy, which is a reason of microcytic hypochromic anemia. Patients with major thalassemia require multiple blood transfusions. This study evaluated growth in thalassemic patient and relationship with ferritin level.

Materials and Methods

This is a cross sectional study on seventy patients (36 boys, 34girls) with transfusion dependent major thalassemia at the special diseases center of Yazd. Their age rang was 2 to 28 year. All of them received chelating therapy (Deferoxamine) every night. Weight, height, body mass index (BMI) and serum ferritin of patients were recorded.

Results

In this study 46 (65.71%) of patients had height less than five percentile, and 24(34.29%) more than five percentile. Thirty eight patients (54.28%) had weight more than five percentile and 32(45.71%) less than five percentile. BMI of 13(18.6%) patients were low and 57(81.4%) patients had normal BMI. Mean serum ferritin in patients with height more than 5 percentile was 2252+/-1040 and with height less than 5 percentile was 2962+/-1606(P-value=0.072). mean serum ferritin in patient with weight more than 5 percentile was 2309+/-1284 and with weight less than 5 percentile was 3199+/-1545 (P-value=0.017). In patient with normal BMI, mean serum ferritin was 2679+/-1378 and it was 2596+/-1777 with low BMI.

Conclusion

High serum ferritin levels during puberty cause delay of growth retardation and development in transfusion dependent thalassemia patients.

Key words

beta-Thalassemia, Growth, Deferoxamine, Blood Transfusion

Corresponding Author

Ghilian, Rozita. MD. Internal Medicine. Hematology oncology and Genetics Research Center Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

Introduction

Beta-thalassemia major is a common inherited hematological disorder in Asia. Almost 100,000 patients with major thalassemia need regular transfusion (1).

Regular red blood cell (RBC) transfusions eliminate the complications of anemia and compensatory bone marrow (BM) expansion, permit normal development throughout childhood, and extend survival. Transfusions result in iron overload, which is fatal without treatment in the second decade of life. Iron-chelating therapy for iron overload is one important part of major thalassemia treatment in last 20 years (2). Endocrine dysfunction is recognized in patients with transfusion dependent thalassemia, which causes by iron overload (3).

The most common endocrine abnormalities in patients with thalassemia include hypogonadotropic hypogonadism, growth hormone deficiency, and diabetes mellitus (3-4). Hypothyroidism, hyperparathyroidism and low levels of adrenal androgen secretion with normal glucocorticoid reserve have been reported (2). Normal rates of prepubertal linear growth is observed in patients with regular transfusion programs, but poor pubertal growth and impaired sexual maturation have been observed in well-transfused patients (5-8). Pituitary dysfunction causes hypogonadotropic hypogonadism, which usually causes abnormal sexual maturation in them (9,10). Primary gonadal failure has also been reported occasionally (11). Growth failure causes by growth hormone (GH) deficiency (hypothalamic and/or pituitary) and hypothyroidism. Delayed sexual maturation and bone disorders cause by DFO toxicity (10-12). Growth retardation may improve with administration of exogenous growth hormone (13). Hyposecretion of adrenal androgen, delay in pubertal development, zinc deficiency, and free-hemoglobin-induced inhibition of cartilage growth have also been implicated in impairment of growth in patients with thalassemia major (2).

The use of iron chelating drugs has been shown to delay the development of iron induced damage of cardiac and liver tissue, resulting in improved survival, but the prevention of endocrine damage is less clear (14). Deferoxamine (DFO) is a siderophore (an iron-binding compound) produced by the bacterium *Streptomyces pilosus*. It is not absorbed after orally and is rapidly cleared; consequently, subcutaneous or intravenous administration is necessary (15).

Iron chelating therapy should be started before clinically significant iron accumulation, when patients have received between 10 and 20 red-cell transfusions. Early initiation of DFO, before the age of 10 years, assures normal puberty in majority of patients (16). However, the initiation of DFO in young age could be associated with bone toxicity, which could decrease growth (17).

This study investigates the effects of long term blood transfusion in thalassemia on growth and finds correlation between serum ferritin level and growth on our patients.

Materials and Methods

A cross sectional study was conducted on Seventy patients (36 boys, 34 girls) with transfusion dependent thalassemia, who were receiving regular blood transfusions at the special diseases center of Yazd. Children with renal disorders, primary skeletal disorders and severe malnutrition were excluded from the study, and cases should have normal liver function tests including aspartate transaminase, alkaline phosphatase, and bilirubin.

Patients' ages were between 2 to 28 years. The median age at the start of transfusion was 6 months (rang 3-120 months) and the mean transfusion requirement was 0.75 U/Kg every year. Chelating therapy consisting of 30 to 50 mg/Kg subcutaneous DFO was received every night. The mean serum ferritin level during study was tested four times in two year. The first Ferritin concentration was 1200 mic/L. All patients were using DFO at least five nights a week by eight to ten hour subcutaneous infusion.

Weight and height (The standing height measurements were obtained using a standard anthropometric technique with a wall-mounted Harpendenstadiometer) were measured as the standard deviation score (SDS) for age and sex. Body weight index (BMI) was calculated. Measurements were taken by a single investigator.

The data was analyzed by SPSS 11.0 statistical software using student t-test. Differences were significant with PV less than 0.05.

Results

Among seventy patient, 34(48.57%) were women and 36 (51.42%) men, which 35 (50%) were younger than 12 years and 35(50%) older than 12years. In this study 46 (65.71%) of patients had height less than five percentile, and 24 (34.29%) more than five percentile. Thirty eight patients (54.28%) had weight more than five percentile and 32(45.71%) less than five percentile. BMI of 13 (18.6%) patients were low and 57(81.4%) patients had normal BMI. Mean serum ferritin level during the study period was 2664 ± 1446 ng/ml. Mean serum ferritin in patients with height more than 5 percentile was 2252 ± 1040 and with height less than 5 percentile was 2962 ± 1606 (P-value=0.072). mean serum ferritin in patient with weight more than 5 percentile was 2309 ± 1284 and with weight less than 5 percentile was 3199 ± 1545 (P-value=0.017). In patient with normal BMI, mean serum ferritin was 2679 ± 1378 and it was 2596 ± 1777 with low BMI.

Discussion

Growth impairment is commonly seen in children with thalassemia with regular blood transfusions and desferrioxamine treatments (18).

Desferrioxamine is used as a subcutaneous (8 to 12 hours) infusion at least five nights a week to achieve optimum iron removal and iron balance. Reports of abnormal linear growth and metaphysical dysplasia observed in children treated with deferoxamine before the age of 3 years have prompted recommendations for later therapy (19). Bone marrow transplantation is an alternative approach in some patients, which obviates long term transfusion and iron chelating treatment. Acceptable short term results have been published (20), and there are few data on the late effects or quality of life in them.

Seventy transfusion dependent thalassemia patients studied for growth disorders and serum ferritin level. Ferritin level calculated each six month for four times.

In our study the mean serum ferritin level was significantly higher in the patients with a final short stature than in those with a normal final height.

The similar study was defined by Hamidah and coworker on 26 prepubertal patients with beta-thalassemia or HbE-beta thalassemia who were transfusion dependent. The mean serum Ferritin level of the thalassemic patients with a height < 3rd percentile was higher compared to patients with a height > 3rd percentile ($4,567.0$ vs. $2,271.0$, P-value = 0.01) (21). Other similar results were reported by Shalitin and coworkers on Thirty-nine patients with thalassemia major with median age of 16.3 yr (range 2–28). They determined the prevalence rates of endocrine complications in thalassemia major patients and correlated them with the degree of iron chelation. Mean serum ferritin level was significantly higher in patients with a final short stature (height <2 SD) than in those with a final height of >2SD (3491 ± 414 ng/mL vs. 2410 ± 278 ng/mL, P-value = 0.05) but in this study found that the final short stature was significantly associated with the quality of chelation therapy during the prepubertal years (22).

In contrast, in study of Grundy and coworkers reported that there was no difference in the SD scores at assessment between the well and poorly chelated groups and thought this is in part due to genetic factors. The ethnic and socioeconomic make up of group, with many living in the inner city, may also be a contributory factor to short stature (3).

In our study the mean serum ferritin level was significantly higher in the patients with a final low weight and BMI than in those with a normal final weight and BMI.

Conclusion

These data suggest that high serum ferritin levels during puberty are a risk factor for growth retardation. Perhaps another possible way of matching controls would be by calculating mid-parental height.

Acknowledgement

The authors would like to thank for Thalassemia ward of Shahid Sadoughi hospital for their highly knowledgeable advices and support in the neuropsychological investigations.

References

1. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med*. 2011 Jan 13;364(2):146-56.
2. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood*. 1997 Feb 1;89(3):739-61. Review. Erratum in: *Blood* 1997 Apr 1;89(7):2621.
3. Grundy RG, Woods KA, Savage MO, Evans JP. Relationship of endocrinopathy to iron chelation status in young patients with thalassaemia major. *Arch Dis Child*. 1994 Aug;71(2):128-32.
- 4 Kwan EY, Lee AC, Li AM, Tam SC, Chan CF, Lau YL, et al. A cross-sectional study of growth, puberty and endocrine function in patients with thalassaemia major in Hong Kong. *J Paediatr Child Health*. 1995 Apr;31(2):83-7.
5. Sklar CA, Lew LQ, Yoon DJ, David R. Adrenal function in thalassemia major following long-term treatment with multiple transfusions and chelation therapy. Evidence for dissociation of cortisol and adrenal androgen secretion. *Am J Dis Child*. 1987 Mar;141(3):327-30.
6. Kattamis C, Touliatos N, Haidas S, Matsaniotis N, Growth of children with thalassaemia: Effect of different transfusional regimens. *Arch Dis Child* 45:1970,45, 502.
7. Costin G, Kogut MD, Hyman CB, Ortega JA. Endocrine abnormalities in thalassemia major. *Am J Dis Child*. 1979;133(5):497-502.
8. Maurer HS, Lloyd-Still JD, Ingrisano C, Gonzalez-Crussi F, Honig GR. A prospective evaluation of iron chelation therapy in children with severe beta-thalassemia. A six-year study. *Am J Dis Child*. 1988; 142(3):287-92.
9. Roth C, Pekrun A, Bartz M, Jarry H, Eber S, Lakomek M, et al. Short stature and failure of pubertal development in thalassaemia major: evidence for hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion. *Eur J Pediatr*. 1997 Oct;156(10):777-83.
10. De Sanctis V. Growth and puberty and its management in thalassaemia. *Horm Res*. 2002;58 Suppl 1:72-9.
11. Oerter KE, Kamp GA, Munson PJ, Nienhuis AW, Cassorla FG, Manasco PK. Multiple hormone deficiencies in children with hemochromatosis. *J Clin Endocrinol Metab*. 1993 Feb;76(2):357-61.
12. De Virgiliis S, Congia M, Frau F, Argioli F, Diana G, Cucca F, et al. Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr*. 1988 Oct;113(4):661-9.
13. Low LC, Kwan EY, Lim YJ, Lee AC, Tam CF, Lam KS. Growth hormone treatment of short Chinese children with beta-thalassaemia major without GH deficiency. *Clin Endocrinol (Oxf)*. 1995 Apr;42(4):359-63.
14. Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. Survival and desferrioxamine in thalassaemia major. *Br Med J (Clin Res Ed)*. 1982 Apr 10;284(6322):1081-4.
15. De Domenico I, Ward DM, Kaplan J. Specific iron chelators determine the route of ferritin degradation. *Blood*. 2009 Nov 12;114(20):4546-51. Epub 2009 Aug 11.
16. Bronspegel-Weintrob N, Olivieri NF, Tyler B, Andrews DF, Freedman MH, Holland FJ. Effect of age at the start of iron chelation therapy on gonadal function in beta-thalassemia major. *N Engl J Med*. 1990 Sep 13;323(11):713-9.
17. De Sanctis V, Katz M, Vullo C, Bagni B, Ughi M, Wonke B. Effect of different treatment regimes on linear growth and final height in beta-thalassaemia major. *Clin Endocrinol (Oxf)*. 1994 Jun;40(6):791-8.
18. Borgna-Pigatti C, De Stefano P, Zante L. Growth and puberty in thalassaemia major. An interim report. In: Sirchia G, Zanella A, eds. *Thalassaemia today: the Mediterranean experience*. Milan: Centro Transfusionale Ospedale Maggiore Policlinico di Milano Editore, 1987: 88-92.
19. Rodda CP, Reid ED, Johnson S, Doery J, Matthews R, Bowden DK. Short stature in homozygous beta-thalassaemia is due to disproportionate truncal shortening. *Clin Endocrinol (Oxf)*. 1995;42(6):587-92.

20. Lucareli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassaemia. *N Engl J Med* 1990; 322: 417-23.
21. Hamidah A, Arini MI, Zarina AL, Zulkifli SZ, Jamal R. Growth velocity in transfusion dependent prepubertal thalassemia patients: results from a thalassemia center in Malaysia. *Southeast Asian J Trop Med Public Health*. 2008;39(5):900-5.
- 22) Shalitin S, Carmi D, Weintrob N, Phillip M, Miskin H, Kornreich L, et al. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. *Eur J Haematol*. 2005 Feb;74(2):93-100.