J. Dhaka National Med. Coll. Hos. 2018; 24 (01): 29-32

Original Article

Assessment of growth and puberty and iron overload in multi-transfused Bangladeshi Thalassemia patients

Belayet Hossain[1], Selimuzzaman[2], W A Khan[3], NilufarAkter Chowdhury[4], Fazlur Rahman[5], A.Wahab[6], Sajeda Sultana[7], Mehedi Hasan[8]

[1]Associate Professor, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka, [2]Professor, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka, [3]Professor, Dept. of Pathology, BICH, Dhaka Shishu Hospital, Dhaka, [4]Registrar, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, [5]Medical Officer, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka, [6]Medical Officer, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka,[7]Medical Officer, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka, [8]Medical Officer, Dept. of Haemato-Oncology, BICH, Dhaka Shishu Hospital, Dhaka.

Abstract

In transfusion dependant Thalassemia patients undergoing transfusion and multiple transfusions along with inadequate chelation therapy leads to iron overload and may cause growth retardation and delayed puberty. The aims of this study are to assay the growth pattern and puberty status and their correlation with iron overload in multi-transfused Bangladeshi Thalassemia patients. This retrospective study assays multi-transfused thalassemic children in Dhaka Shishu(Children) Hospital Thalassemia Centre of Dhaka Shishu(Children) Hospital. Out of total 135 patients, the age range was 12-18 years and mean age of the patients was 14.6 ± 2.5 years and 72(53%) were boys and 63(47%) were girls. The mean weight was 32.25 kg ± 8.45 kg, the mean height was 136.22 cm ± 11.57cm and 81(60.1%) patients were found short with height less than 5th percentile for age. Of the 81 short cases 52 were boys and 29 were girls. Ninety three (69%) cases had delayed puberty, among them boys were 48 (67.6% of boys) and girls were 45 (70.3% of girls). Majority of the girls having primary amenorrhea with few of them having delayed menarche. Of the 93 delayed puberty cases, 61(65.6%) were of short stature and 32(34.4%) were of normal height. The high prevalence of growth retardation and delayed puberty in this study justify the need for vigilant clinical evaluation of multi-transfused thalassemic children for early detection and appropriate treatment of growth retardation and delayed puberty.

Key words: Thalassemia, multi-transfusion & growth and puberty.

Introduction

Thalassemia is one of the most common hereditary diseases worldwide. It is an important health problem, causing much morbidity, early mortality and a lot of financial and emotional misery for a family.[1]

Thalassemia is an important health problem in Bangladesh. Dhaka Shishu (Children) Hospital Thalassemia Center (DSHTC) has diagnosed 901 β-thalassemia major and 2407 Hb E- β thalassemia in the last decade (data of DSHTC). About 30-40 thalassemia patients are getting Integrated management including blood transfusion in Dhaka Shishu (Children) Hospital Thalassemia Center (DSHTC) daily. These thalassemia patients come from all over the country.

Blood transfusion is essential for survival of thalassemic children while eventually leading to iron overload, resulting in various endocrine dysfunctions[2,3,4,5] Several authors have been studied over multitransfused and untransfused thalassemia patients with the findings of high incidence of growth disturbances and endocrine dysfunction.[6,7] Recently various authors have reported high incidences of growth retardation, delayed puberty and endocrine dysfunctions in multitransfused thalassemic patients.[8,9,10]

In Bangladesh, more than 1000 cases of thalassemia are born every year according to conservative data of WHO, yet no published data is available on the growth, puberty and endocrine status of these children.

This study was conducted to assess the growth, puberty and iron overload in multi-transfused Bangladeshi thalassemia patients.

OBJECTIVE

To assess the growth, puberty and correlation with iron overload in multi-transfused Bangladeshi thalassemia patients.

MATERIALS AND METHODS

Study design

Cross sectional study.

Study place
Dhaka Shishu (Children) Hospital Thalassemia Center, Dhaka Shishu (Children) Hospital. Dhaka, Bangladesh.

Study period
1st January, 2016 to 31st May 2017.

Sample size
135 (63 females and 72 males).

Inclusion criteria
Hemoglobin E- β Thalassemia & β Thalassemia Major patients.

Age 12-18 years.

Registered in Dhaka Shishu(Children) Hospital Thalassemia Center.

Multitransfused.

Exclusion criteria
Age below 12 and above 18 years.

Patients with other chronic illness.

Operational definitions
Delayed puberty in female: Absence of breast development by 13 year.

Delayed puberty in males: Absence of testicular enlargement <5 ml by 14 year.

Primary amenorrhea: Absence of menarche by 16 year.

Secondary amenorrhea: Absence of menses for 6 months after having regular menses previously.

Short stature: Height less than 5th centile for age as per standard growth charts.

Procedure
Growth assessment was done by measuring weight and height.

Pubertal staging was done by Tanner SMR.

Testicular volume was measured by Sonographic measurement.

Biochemical investigations like Serum ferritin was estimated by Chemiluminescence methods.

Statistical analysis
Data were analyzed using SPSS (version 16.0).

Numerical data were represented as mean ± SD and mean comparison were done by unpaired T test.

Proportions were compared using the Chi-square test.

Confidence intervals were set at 95 and p value <0.05 was taken as significant.

Patient's characteristics
Male : 72 (53%)
Female : 63 (47%)
Mean age : 14.6 ± 2.5 yrs

Iron Chelating agents used:
- On Deferipon : 65 (48%)
- On Desferrioxamine : 20 (15%)
- On both : 16 (12%)
- On Deferasirox : 28 (21%)
- On none : 06 (04%)

Transfusion history:
- Well transfusion : 44 (32.6%)
- Under transfusion : 91 (67.4%)

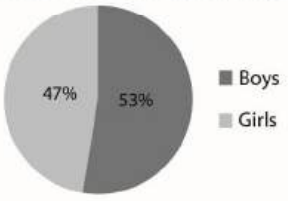
Mean blood transfusion requirement was 190 ± 14 ml/kg/yr, with a range of 155 to 224 ml/kg/yr.

Results
In this study of total 135 patients, the age range was 12-18 years and mean age of the patients was 14.6 ± 2.5 years (Table-I) and 72(53%) were boys and 63(47%) were girls (Fig-I).

Table-I: Age and sex distribution of studied subjects (n=135).

Variable	Mean ± SD/frequency	Range
Age	14.6 ± 2.5 years	12-18 years

Figure-I: Sex distribution of studied subjects (n=135).



Among the total 135 cases 44 (32.6%) were well transfused and 91(67.4%) were under- transfused.

Regarding anthropometric measurement of 135 studied subjects, the mean weight was 32.25 kg ± 8.45 kg, the mean height of was 136.22 cm ± 11.57cm and 81(60.1%) patients were found short with height less than 5th percentile for age. Of the 81 short cases 52 were boys and 29 were girls (Table-II).

Table-II: Anthropometry of studied subjects (n=135).

Parameter	Mean ± SD/frequency
Standing height	136.22 cm ± 11.57 cm
Weight	32.25 kg ± 8.45 kg
Short	81 (60.1%)
Boys	52
Girls	29

The mean serum ferritin level of all 135 cases was 4160 ± 2240 ng/ml (range 764-9273 ng/ml). The short children had mean ferritin level of 4281 ± 1636 ng/ml and normal height children had mean ferritin level of 4325 ± 2174 ng/ml. There was no statistical significance correlation between height and serum ferritin level (P value=0.40) (Table–III).

Table-III: Serum ferritin level in normal and short children

	Mean Serum ferritin level ng/ml	Range of ferritin level ng/ml	P value
All children (n=35)	4160 ± 2240	764-9273	
Normal children	4325 ± 2174		0.34
Short children	4281 ± 1636		

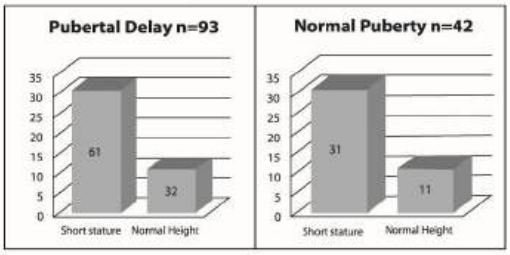
As regard puberty, there were 93 (69%) cases had delayed puberty, among them boys were 48 (67.6% of boys) and girls were 45 (70.3% of girls). Majority of the girls having primary amenorrhea with few of them having delayed menarche.. The difference of serum ferritin level in delayed puberty and normal puberty was not statistically significant (Table-IV).

Table-IV: Pubertal status of the study subject (n=135).

Pubertal delay (n=93, 69%)		Normal puberty (n=42, 31%)		
Boys 48 (67.6% of boys) (Testicular volume < 5 ml, Mean testicular volume of all was 7.89 ml, range 3-18 ml)	Girls 45 (70.3% of girls) (Primary amenorrhea and delayed puberty)	Boys 23 (32.4%)	Girls 19 (29.7%)	
Serum Ferritin: 4573 ± 2059 ng/ml		Serum Ferritin: 3831 ± 1784 ng/m		P value 0.43 NS

Of the 93 delayed puberty cases 61(65.6%) were of short stature and 32(34.4%) were of normal height (Figure-II).

Figure-II: Anthropometry of delayed pubertal cases (n=93) and normal pubertal cases (n=42).



Discussion

Thalassemia patients are suffered from chronic anaemia, so blood transfusion for Thalassemia patients to maintain hemoglobin level in normal range is essential in order to prevent deleterious effects of anaemia.[11,12] Multi-transfusion leading to iron overload in Thalassemia patients is another important cause of endocrine dysfunction and growth failure. So effective iron chelation is essential for reduction iron deposition in various endocrine glands.[13] So transfusion and iron-chelation therapy are critical for prolonging life and improving quality of life. Growth failure in thalassemia is multifactorial in etiology. Chronic anaemia, hypersplenism, chronic liver disease, nutritional deficiency and hormone dysfunctions due to iron toxicity have been implicated as major causes of growth retardation. Adequate transfusion and aggressive chelation therapy are initiated early in life to ensure a favorable prognosis for life.[14,15]

In this study, majority of the study cases (67.4%) were under transfused might be due to poor socioeconomic background, illiteracy and lack of adequate transfusiom facilities in nearby health centers.

This study showed, 81(60.1%) patients were short with height less than 5th percentile for age which is comparable to the reported incidence all over the world,[6,16] higher than the finding of the study done by Hashemi A MD et al where the incidence of short stature was 44.9%.[17] There was no correlation between iron overload (serum ferritin) and short stature (p value = 0.37) indicating other factors like chronic anaemia & hypoxia, chronic liver disease, zinc & folate deficiency, hormonal dysfunction, intensive use of chelating agents and emotional factor, under nutrition and hyper metabolic status may play a role in growth retardation rather than hemosiderosis alone.[6,8,19]

As regard puberty, there were 93 (69%) cases had delayed puberty, among them boys were 48 (67.6% of boys) and girls were 45 (70.3% of girls), majority of the girls having primary amenorrhea which correlates and/or close to the studies done by different authors,[6,20,21,22] but higher than the study done in Iran and Italy.[19,23] Of the 93 delayed puberty cases 61 (65.6%) were of short stature and 32 (34.4%) were of normal height. There is no statistical correlation between pubertal status and serum ferritin level indicating factors responsible for organ damage include; chronic anaemia & hypoxia, increase collagen deposition secondary to increased activity of iron dependant procollagen proline hydroxylase enzyme with

subsequent disturbed microcirculation in various endocrine glands, hormonal dysfunction, intensive use of chelating agents and emotional factor, lack of pubertal growth spurt, under nutrition and hyper metabolic status may play a role in delayed puberty in addition to hemosiderosis.[6,18,19,24]

Conclusion

This study supports the fact that the thalassemic children are growth retarded and have delayed puberty which usually begin early in life along with under transfusion and iron overload.

Recommendation:

Optimum blood transfusion, control of iron overload, and regular endocrine evaluation for early detection and treatment of associated complications are mandatory for their normal growth, quality of life and life expectancy.

Referance:

1. El-Beshlawy A, Youssry I. Prevention of hemoglobinopathies in Egypt. Hemoglobin. 2009; 33(supl):14-20.
2. Cummingham MJ, Maclin EA, Neufil EJ, Cohen ER. Complications of beta Thalassemia major in North America. Blood 2004;104:34-9.
3. Fosburg MT, Nathan DG. Treatment of Cooly`s anemia.Blood 1990;76(3):435-44.
4. Hoffbrand AV,Wonke B. Iron chelation therapy. J Intern Med Suppl. 1997; 740: 37-4.
5. Najafipur F. Evaluation of Endocrine Disorders in Patients with Thalassemia Major. Int J Endocrinol Metab. 2008;2: 104-113.
6. Rashid H. Merchant, Amruta Shirodker, Jabed Ahmed. Evaluation of growth, Puberty and endocrine dysfunctions in relation to iron overload in Multi Transfused Indian Thalassemia patients. Indian J Pediatr. 2011;78(6); 678-683.
7. Anita Saxena. Growth retardation in Thalassemia major patients. Int J Hum Genet. 2003; 3(4): 237-246.
8. Aydinok Y, Darcan S, Polat A. Endocrine complication in patients with Beta-thalassemia major. J Trop Pediatr. 2002; 48: 50-54.
9. Lo L, Singet ST. Thalassemia, Current approach to an old disease. Pediatr Clin North Am. 2002; 49: 1165 -91.
10. Borgna-Pigmati C, De Stifano P, Zonta L. Growth and sexual maturation in thalassemia major. J Trop Pediatr. 1985; 106: 150-155.
11. Nathan DG. Pioneers and modern ideas. Perspectives on thalssemia. Pediatrics. 1998;102 :281-3: discussion 288-9.
12. Borgna-Pignatti C, Rugolotto S, De Shefano P, Zhao H, Cappelini MD, Del Vecchino GC, et al. Servival and complications in patients with Thalassemia major treated with transfusion and deferrioxamine . Hematologica 2004;89:1187-93.
13. Berkovitch M, Bristritzer T, Milone SD, Perlman K, Kucharczyk W, Oliverieri NF. Iron deposition in in the anterior pituitary in homozygous beta-thalassemia: MRI evaluation and correlation with gonadal function.J Pediatr Endocrinol Metab. 2000;13(2) :179-84.
14. De Virgilis S, Cossu P, Toccafondi C, Samma G, Frau F,Lubrano R, et al. Effect of subcutaneous desferrioxamine on iron balance in young Thalassemia major patients. Am J Pediatr Hematol Oncol. 1983 Spring 5(1):73-7.
15. Fargion S ,Tadiei MT, Gabutti V, Piga A, Di Palma A, Capra L, et al. Early Iron overloas in beta-thalassemia major ,when to start chelation therapy? Arch Dis Child. 1982 Dec;57(12):929-33.
16. George A, Bhadun A,Sen S Chowdhury VP. Physical growth in thalassemic children. Indian J Pediatr 1997 ;64 : 64-71.
17. Hashem A MD, Hashemian Z MD, Ordoni M MD, Amanat M MD,Purshamshi F MD, Gashemi M Phd. Endocrine Dysfunctions in Iron Overload in Patients with Major Thalassemia. Iranian Journal of Pediatric Hematology . 2012; Vol 2. No 2.: 60-66.
18. Skordis N. The growing child with Thalassemia. J Pediatr Endocrinol Metab. 2006; 19: 467-9.
19. De Sanctis V, Roos M, Gasser T, Fortini M, Raiola G, Galati MC. Italian Working Group on Endocrine Complecations in Non-Endocrine Diseases Impact of long-term iron chelation therapy on growth and endocrine functions in Thalassemia. J Pediatr Endocrinol Metab. 2006 Apr; 19(4): 471-80.
20. Low LC. Growth of children with beta-thalassemia major. Indian J Pediare. 2005; 72: 159-64.
21. Najafipur F. Evaluation of Endocrine Disorders in Patients with Thalassemia Major. Int J Endocrinol Metab. 2008; 2: 104-113.
22. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M et al. Metabolic and endocrinologic complications in Beta-thalassemia major : a multicenter study in Tehran. BMC Endocr Disorder 2003; 3; 4-8.
23. Fatemeh Saffar, Abolfazl Mahyar, Shabnam Jalilolgadr. Endocrine and Metabolic disorders in beta Thalassemia major patients. Caspian J Intern Med. 2012; 3(3): 466-472.
24. Iancu T. Ultrastructural pathology of iron overload with special reference to endocrine glands. In: Pintor C, Corda R, De Sanctis V, editors. Workshop on endocrine problems in Thalassemia venezia: San Marco Scientific Publications: 1990: 19-28.