International Journal of Contemporary Pediatrics
Jadhav SS. Int J Contemp Pediatr. 2023 Aug;10(8):1205-1210
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20232235

Original Research Article

Growth profile of children with beta-thalassemia major

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Received: 05 July 2023
Revised: 15 July 2023
Accepted: 20 July 2023

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ABSTRACT

Background: Retarded growth in thalassemic patient is complex and multi-factorial, it includes chronic hypoxia secondary to anemia when pre-transfusion haemoglobin is below 9 g/dl. Development of secondary sexual characteristics in thalassemic children is markedly delayed as compared to their non-thalassemic siblings and to the expected development criteria due to chronic hypoxia and iron overload. The main objective of the present study is to monitor the growth of these patients longitudinally
Methods: This was a observational, cross sectional field study in Pune, Maharashtra.
Result: Patients with beta-thalassemia major on regular blood transfusions have growth failure, deranged liver function and hypocalcaemia in conjunction with high serum ferritin levels
Conclusions: Beta thalassemia major, having the potential of leading to multisystemic complications, is a chronic disease that should be treated and followed-up by a multidisciplinary approach

Keywords: Anemia, Thalassemia, Ferritin, Iron overload

INTRODUCTION

Thalassemia is a blood disorder passed down through families (inherited disorders). In 1925, Thomas Cooley and Pearl Lee described this form of severe anemia, occurring in children of Italian origin and associated with splenomegaly and characteristic bone changes.[1] Because all early cases were reported in children of Mediterranean origin, the disease was later termed thalassemia, from the Greek word for sea, thalassemia.[2]

Their clinical severity widely varies, ranging from asymptomatic forms to severe/even fatal entities. Retarded growth in thalassemic patient is complex, multi-factorial, it includes chronic hypoxia secondary to anemia when pre transfusion Hb below 9 g/dl. Development of secondary sexual characteristics in thalassemic children is markedly delayed as compared to their non-thalassemic siblings and to expected development criteria due to chronic hypoxia and iron overload.

The paucity of the data in our population prompted us to plan this study aiming to assess the growth parameters in children receiving packed red cells transfusion with chelation therapy.[3] The main objective of the present study is to monitor the growth of these patients longitudinally.

Need of study

The clinical manifestation of the endocrine abnormalities occurs late in life, so most of the studies available are done on adults. Also, scarcity of Indian data warrants a study. The cost of chelation prevents ideal therapy for majority of the patients and the compliance with transfusion is often not optimal.

Therefore, there is a possibility that there may be high prevalence of puberty related issues in such patients and there is a high chance of those issues beginning at an early age. In view of non-availability of Indian studies

and the increasing concern among the patients regarding their stature there is a need to look into and monitor the growth profile of these patients.

METHODS

Study type was observational, cross sectional field study. Study place was Bharati Vidyapeeth medical college and hospital, Pune and study period was December 2021-April 2023.

Inclusion criteria

Thalassemia major children who had received blood transfusion since the age of diagnosis and those children receiving transfusion should be > or equal to 5 years of age but <15 years of age at the time of enrolment were included.

Exclusion criteria

Children with primary diagnosed endocrinopathy, thalassemia intermedia and minor, children on any hormonal replacement therapy and children with chronic illness not related to thalassemia major were excluded from the study.

Procedure

All diagnosed cases of thalassemia who are in the age of 5 years to 15 years were screened. After obtaining written informed consent from the parent's and assent from children above 12 years of age, detailed history was obtained and documented in relation to the demographic data, age of diagnosis, frequency of transfusion, compliance to transfusion and chelation. Growth parameters such as height and weight, and biochemical parameters like blood sugar levels, liver function tests serum ferritin, and free T_3, T_4, TSH and calcium profile was assessed and documented at first as well as third visit.

Weight

Weight was measured in standing position with clothes using a standard electronic weighing scale with a minimum measurable weight of 10 grams at every visit. (Name of company-Zeal medical Pvt limited). Measurements obtained at the end of every 2 months was plotted on affluent growth charts for boys as well as girls, 2007.

Height

Height was recorded in standing position without socks with the help of a standard stadiometer at an interval of six months with the lower reading of 0.1 cm and plotted on the affluent growth charts for the boys as well as girls, 2007.

Hemoglobin levels

Pre and post blood transfusion, patients' blood sample was sent for hemoglobin levels.

Biochemical parameters

Following tests were done in all the patients-serum ferritin levels, serum TSH, free T_4, T_3, calcium profile, liver function tests.

Bone age

An X-ay of the wrist joint of the non-dominant hand was done annually.

Data entry

Detailed history obtained in relation to the demographic data, age of diagnosis, frequency of transfusion, compliance to transfusion and chelation was documented. The results of anthropometric parameters so obtained at specific intervals was collected and plotted on affluent growth charts for boys and girls, 2007. All laboratory investigations were obtained and data was compiled on Microsoft excel sheets for analysis

Ethical approval

Ethical clearance was obtained from institutional ethical committee.

Statistical analysis

All the data collected will be entered into Microsoft excel sheets and were analysed using SPSS. Descriptive statistics with respect to obtained parameters was used.

RESULTS

The total number of children in this study were 27. There were 9 girls while the boys were 18, slightly more and comprised of 66.67% of the total sample population.

Table 1: Age and Sex wise distribution of children.

Age (In years)	Boys	Girls	Total
5	3	2	5
6	3	1	4
7	3	1	4
8	1	1	2
9	1	0	1
10	3	2	5
11	1	0	1
12	0	0	0
13	1	0	1
14	2	1	3
15	0	1	1
Total	18	9	27

Visit 1 growth parameters and their interpretation according to world health organization charts

A 22.22% of our patients were stunted (height z-score <-2). 22.22% of our patients were underweight (z-score <-2). 11.11% had normal weight (weight z-score <-1) and 3.70% were severe underweight (weight z-score <-3). BMI was normal in the 55.56% of our patients (z-score <-1).

Table 2: Height, weight and BMI wise distribution of children.

Z score	Height 1		Weight 1		BMI 1	
	N	%	N	%	N	%
>3	0	0.00	0	0.00	0	0.00
>2	0	0.00	0	0.00	0	0.00
>1	0	0.00	0	0.00	0	0.00
0	7	25.93	3.0	11.11	11	40.74
<-1	12.0	44.44	17.0	62.96	15.0	55.56
<-2	6.0	22.22	6.0	22.22	1.0	3.70
<-3	2	7.41	1	3.70	0	0.00

Visit 3 growth parameters and their interpretation according to world health organization charts

The 36.36% of our patients were stunted (height z-score <-2). 22.73% of our patients were underweight (z-score <-2). 59.09% were normal (weight z-score <-1) and 4.55% were severe (weight z-score <-3). BMI was normal in 50% of our patients (z-score <-1).

Table 3: Height. weight and BMI wise distribution of children.

Z score	Height 3		Weight 3		BMI 3	
	N	%	N	%	N	%
>3	0	0.00	0	0.00	0	0.00
>2	0	0.00	0	0.00	0	0.00
>1	0	0.00	0	0.00	0	0.00
0	5	22.73	3.0	13.64	11	50
<-1	7.0	31.82	13	59.09	11	50
<-2	8.0	36.36	5.0	22.73	0.0	0.00
<-3	2	9.09	1	4.55	0	0.00

Liver function test

Liver function test done in all patients were persistently deranged at first and third visit. Mean SGOT levels were reduced on third visit (54±52.39 IU/L) as compared to first visit (65.56±67.59 IU/L). Mean SGPT levels were reduced on third visit (49.50±66.43 IU/L) as compared to first visit (54.96±53.66 IU/L).

Calcium total

The mean total serum calcium was 8.738±0.7133 mg/dl at first visit and 8.828±0.8970 mg/dl at third visit.

Table 4: SGOT at first and third visit.

SGOT (IU/L)	SGOT-1	Female SGOT-1	Male SGOT-1	SGOT-3	Female SGOT-3	Male SGOT-3
No. of patients	27	9	18	22	7	15
Minimum	17.00	25.00	17.00	22.00	25.00	22.00
Maximum	332.0	332.0	184.0	280.0	280.0	75.00
Mean	65.56	88.67	54.00	54.00	73.29	45.00
Std. deviation	67.59	97.74	45.46	52.39	91.86	15.09

Table 5: SGPT at first and third visit.

SGPT (IU/L)	SGPT-1	Female SGPT-1	Male SGPT-1	SGPT-3	Female SGPT-3	Male SGPT-3
No. of patients	27	9	18	22	7	15
Minimum	10.00	16.00	10.00	11.00	27.00	11.00
Maximum	229.0	229.0	182.0	336.0	336.0	74.00
Mean	54.96	69.33	47.78	49.50	78.71	35.87
Std. deviation	53.66	72.48	42.03	66.43	113.6	21.49

Table 6: Calcium total at first and third visit.

Variables	Calcium total 1	Female calcium total 1	Male calcium total 1	Calcium total 3	Female calcium total 3	Male calcium total 3
No. of patients	27	9	18	22	7	15
Minimum	7.240	7.240	7.700	7.250	7.250	7.680
Maximum	10.10	10.10	9.700	10.70	10.10	10.70
Mean	8.738	8.630	8.792	8.828	8.829	8.827
Std. deviation	0.7133	0.8560	0.6512	0.8970	1.036	0.8642

Serum ferritin

Mean serum ferritin levels at first visit were 3591±2137 ng/ml and 4293±2058 ng/ml at third visit

Table 7: Serum ferritin at first and third visit.

Serum ferritin	Serum ferritin 1	Serum ferritin 3
No. of patients	27	22
Patients	9.693	10.10
Maximum	8628	7461
Mean	3591	4293
Std. deviation	2137	2058

Serum ferritin correlation

When serum ferritin levels were correlated with liver enzyme, we found that serum ferritin increases to large extent and it continues to rise as SGPT and SGOT increases. When we correlated serum ferritin levels with liver enzymes, we found a positive correlation. As the serum ferritin level increases, the levels of SGOT and SGPT rise significantly

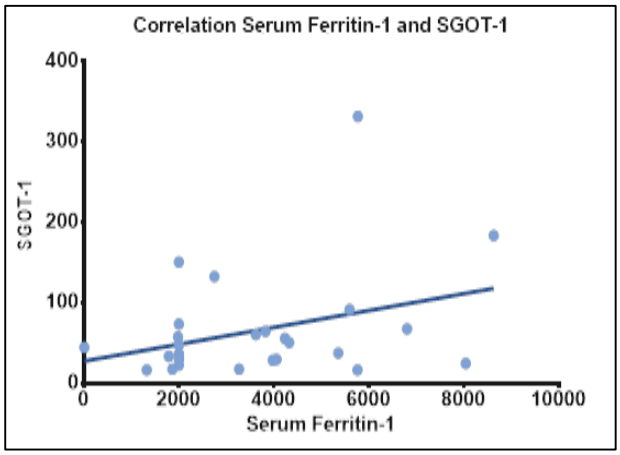

Figure 1: Correlation of serum ferritin 1 with the SGOT 1.

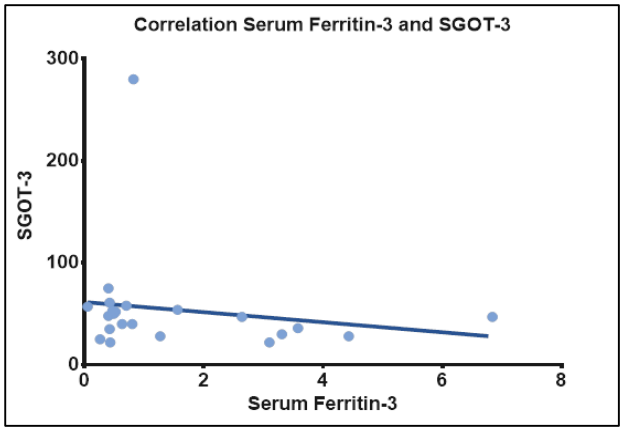

Figure 2: Correlation of serum ferritin 3 with the SGOT 3.

Bone age

In this study, the mean bone age of patients were close to their chronological age.

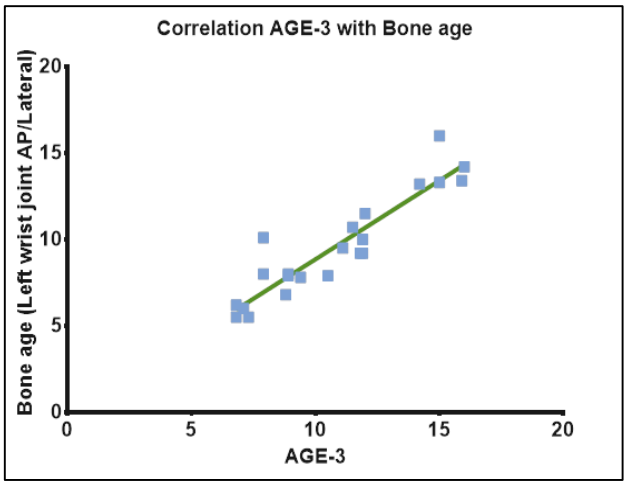

Figure 3: Correlation of AGE 3 with bone age.

DISCUSSION

Assessment of growth parameters is an important tool for evaluation of nutritional status of a child, when done for a large group of children together, who share many characteristics like ethnicity, similar socioeconomic environment, it gives an idea of how the children of an entire community are growing. The burden of β-thalassaemia is not uniform with some communities having much higher frequencies ranging from 5 to 17%.[4,6] There is no population based large study from Pune.

Gender

In our study, there were 9 female and males were 18, slightly more and comprised of 66.67% of the total sample population. The distribution of thalassemic patients according to sex shows male predominance with sex ratio of 2:1 such difference was also noted in other studies. Some of the other studies done in other parts of India have reported 65.5, 62.1 and 56 % of male patients.[7-8] This might be due to the gender bias among the parents of these ill children who seek medical care and are ready to spend more for their male children only.

Age

Most of the children visiting the hospital for their transfusion needs were in the age group of 5-15. This can be explained by the fact that if children are not transfused, they die before the age of 6 years and if they are transfused and non-chelated, they die before the age of 20.[8] It also important for the hospital and health authorities to know the age group of the effected patients while they are creating facilities for these patients.

Height, weight and BMI

Growth failure is common in patients with thalassemia. It is multifactorial in thalassemia, related to chronic hypoxia due to chronic anemia, chelation toxicity, low serum zinc level, hepatic iron overload with hepatic dysfunction and iron associated endocrinopathies such as hypogonadism, hypothyroidism, and growth hormone deficiency.[9-11] Several studies reported a higher incidence of growth abnormalities in children with Thalassemia major. In our study the mean height of our patients was significantly lower. At visit 1st and 3rd visit 22.22%, and 36.36% of patients were stunted (height z-score<-2, 3 percentile), respectively. This is in agreement with previous reports, Hashemi et al found 65.71% of thalassemic patients had height <5th percentile.[12] Vogiatzi et al, found 25% were of short stature (height z-score <-2).[12] Jain et al reported 28% of patients had height <5th percentile.[13] Huang et al reported 24 patients (48%) were of short stature with height under the 3rd percentile.[14] Among them, 15 cases presented with their height and weight both under the 3rd percentile.

Regarding body weight; at visit 1st, 22.22% of our patients were underweight (z-score <-2); 11.11% were normal (weight z-score <-1) and 3.70% were severe (weight z-score <-3). At visit 3rd, 22.73% of our patients were underweight (z-score <-2); and 4.55% were severe (weight z-score <-3). Regarding BMI; at visit 1st and 3rd visit BMI was normal in 55.56% (z-score <-1), 48.15% (z- score=0), 50.00% (z-score <-1) and 40.91% of our patients (z-score <-1), respectively. Our findings were in agreement with previous studies; Hashemi et al. reported underweight in 45.71% and Jain et al found 20% were underweight in patients with thalassemia major.[12,13] Huang et al reported 15 cases presented with their weight under the 3rd percentile.[14] A study by Saxena et al supported the fact that thalassemic patients are short, have low rate of growth and BMI, which was related to low hemoglobin and high ferritin levels and sub-optimal iron chelation therapy.[15]

SGOT and SGPT

Liver enzymes such as SGOT, SGPT are raised in transfusion dependent β-thalassemia major patients. Though liver biopsy is gold standard test to know iron overload state in liver but it is invasive method and T2 MRI is best non-invasive method of determining liver iron. This study was planned to study the correlation of liver enzymes (SGOT and SGPT) with serum ferritin levels in children with transfusion dependent β-thalassemia major. Serum level of SGOT >50 IU/L and SGPT >40 IU/L were considered abnormal. In our study, the mean SGOT at 1st and 3rd visit were 65.56±67.59 and 54.00±52.39, i.e., abnormal. Similarly, SGPT at first and third visit were 54.96±53.66 and 49.50±66.43, which were higher than normal value ($p<0.05$). Jain et al reported the mean level of liver enzymes SGOT was 117±35.5 IU/L, SGPT was.0 151±47.2 IU/L.[13]

Serum ferritin levels and its correlation with other parameters

High serum ferritin levels during puberty cause delay of growth retardation. Hashemi et al reported high serum ferritin levels during puberty cause growth retardation and development in transfusion dependent thalassemia patients.[12] The mean serum ferritin level was 3591±2137 and 4293±2058 at 1st and 3rd visit, respectively. Suman et al reported mean serum ferritin was 2130±859.85 ng/ml.[16] When serum ferritin levels were correlated with liver enzyme, we found that serum ferritin increases to large extent and it continues to rise as SGPT and SGOT increases. When we correlated serum ferritin levels with liver enzymes, we found a positive correlation. As the serum ferritin level increases, the levels of SGOT and SGPT rise significantly. Shams et al noted the similar findings from study in Iran with significantly raised liver enzymes (ALT, AST) in homozygous thalassemia major patients than in controls.[17] Suman et al observed during a study that some disturbances occur in liver functions in hepatitis negative thalassemia patients with iron overload.[16] Barton et al noted similar results as serum ferritin increases liver enzymes also increases.[18]

Correlation of AGE-3 with bone age

Thalassemia patients are in need of frequent assessment of bone age because of growth failure and pubertal disorders. In our study, the mean bone age of patients was close to their chronological age.

Calcium homeostasis

Disturbance of calcium homeostasis is also known in thalassaemia major that could be due to hypoparathyroidism. The serum calcium level was significantly lower in our patients than that of normal range. Our results was in agreement with Shamshirsaz et al, Zamboni et al, Aleem et al, and Vogiatzi et al who found hypocalcemia in their thalassemic patients.[9,19,20,21]

They explained their results by the presence of iron overload and hemosiderosis resulting in endocrinopathies. Chelation therapy in addition to cirrhotic changes due to hemosiderosis may also play a significant role in hypocalcemia.

Limitation

Limitation of this study was that it did not included controls which could have better given us comparative results as compared to normal subjects.

CONCLUSION

Beta thalassemia major, having the potential of leading to multisystemic complications, is a chronic disease that should be treated and followed-up by a multidisciplinary approach. Due to frequently encountered

endocrinological complications, this study reflects the need for beta thalassemic patients to be followed-up regularly by hematology and endocrinology departments in coordination.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jadhav SS. Growth profile of children with beta-thalassemia major. Int J Contemp Pediatr 2023;10:1205-10.