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Original Research Article

A study of growth pattern in regularly transfused thalassaemic children of age group of 2 years to 12 years

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ABSTRACT

Background: ß-thalassemia is an autosomal recessive single gene disorder. Physical growth failure is one of the most important complications of thalassemia. Very few data regarding growth pattern of thalassemic children is available from India especially North East part. Keeping this in mind, present study was undertaken. To study the growth pattern of transfusion dependent thalassaemic children and to compare growth pattern between regularly and irregularly transfused children.
Methods: A cross-sectional observational study was done on 38 thalassaemic patients (aged 2 years-12 years) who attended Department of Pediatrics, Assam Medical College Dibrugarh. History, physical examination and investigations were done and filled in predesigned proforma. Anthropometric measurements like weight and height were taken from all patients. Sexual maturity rating was done in girls ≥10 years and boys ≥11 years. Lab parameters included pre-transfusion hemoglobin (Hb), serum ferritin, LFT, RFT, Thyroid profile. Percentile for weight, height and body mass index were calculated using WHO (2007) reference data. Collected data were compared with age and sex matched normal children.
Results: About 34.21% transfusion dependent children had under-nutrition and 50% had stunting. 42% had thinness. Stunting was more in irregularly transfused children (81.25%) as compared to regularly transfused children which was highly significant ($p<0.001$). Under-nutrition among irregularly transfused children was more (40%) compared to regularly transfused children (28.57%). Pubertal spurt was delayed in 66% children. Those who had Hb <5 gm/dl had 100% stunting and under-nutrition.
Conclusions: Regular blood transfusion with growth monitoring and appropriate iron chelation (Sr. Ferritin >1000 ng/ml) is of utmost importance in transfusion dependent thalassaemic children.

Keywords: Growth, Thalassemia, Transfusion

INTRODUCTION

The inherited hemoglobin disorders are the most common single gene defect in man. The prevalence of hemoglobinopathies is on the rise worldwide. The frequency of the carrier state has been estimated to be 270/million with about 400,000 annual births a year of infants with serious hemoglobinopathies. This is of special importance in developing countries, where it increases the burden of health care delivery systems.[1]

Hb A (α2ß2), is the predominant adult hemoglobin and normally constitutes approximately 96% of the total adult hemoglobin. A minor adult HbA2 (α2δ2) constitutes less than 3.5% of total adult hemoglobin. Clinically, its major importance is its value in diagnosing ß-thalassemias.[2]

Thalassemia has a spectrum of clinical severity which is

associated with ineffective erythropoiesis, bone marrow expansion and rapid destruction of erythrocytes. Anemia demands frequent blood transfusions. Hemosiderosis and other complications of the disease require a continuous and distressing treatment regime that includes iron chelation treatment, regular medical supervision, frequent admissions to the hospital and on many occasions' surgery. This autosomal recessive anemia in infancy is fatal without transfusions and is fatal in adolescence even with them. The only curative treatment for this disease is bone marrow transplantation (BMT) which is expensive and has a variable success rate of 60-70%.[3]

Growth failure in thalassaemia major (TM) has been recognised for many years and has persisted despite regular blood transfusion and other major therapeutic advances. During the last decades therapeutic progress and bone marrow transplantation resulted in a prolonged life expectancy in thalassemia major patients. Growth retardation, however, continues to be a significant challenge in these individuals, often affecting their social adjustment and quality of life. There are only a few thalassemia units, where these children are regularly given blood transfusions and monitored for various parameters.[4]

A close monitoring of growth pattern may lead to early identification and treatment of these complications to ensure that patients achieve near normal adult height.[5]

Growth and development of children with thalassaemia

Abnormal growth resulting stunting and delayed or absent puberty is characteristic of children with Thalassemia major. Normal growth of β-thalassemia children during the first 10 years of life depends upon the maintenance of haemoglobin levels above 8.5 g/dl. During this period of the child's life hypoxia may be the main factor retarding growth, and the maintenance of haemoglobin levels above 10-11 g/dl together with adequate iron chelation therapy makes the β-thalassemia patients indistinguishable from their non-thalassemic peers.[6]

After the age of 10, even though, adequate levels of haemoglobin are maintained, many of the β-thalassemia children start having decelerated growth. In the pubertal children there may be a reduced growth spurt with marked deceleration, for which iron overload may be responsible. In this age group truncal shortening, most likely due to hypogonadism secondary to iron deposition may also be found[7]. The hormonal cause of growth retardation in β-thalassemia children is complex. Besides hypothyroidism and hypogonadism it become apparent that Growth hormone (GH) also plays a role in their abnormal growth. The β-thalassemia patients may have subnormal spontaneous GH secretion and an impaired GH response to GH-releasing hormone.[8]

Undernutrition is also an important cause of low IGF: I and associated growth disturbances in this group. This may be compounded in certain cases of undernutrition by zinc deficiency.[9]

Problem in India

In India over 20 million people have thalassemia gene. The prevalence of the gene varies between 3 to 18% in north and 1 to 3% in south with certain communities like Sindhis, Kutchis, Lohanas, Bhanushalis, Punjabis, Mahars, Agris, Gouda, Saraswats, etc. showing a high prevalence.[10]

It has been estimated that over 6000-8000 children, who are homozygotes of ß-thalassemia are born in India every year and unfortunately most of these children die either undiagnosed because of inadequate facilities, poor management and/or financial problems.[11]

Data is available only from few centres and as such no statistics are available regarding their growth pattern. India has a large number of young patients with transfusion dependant thalassemia and very few studies have reported the issues related to physical growth in children. Keeping this in mind, present study is undertaken with the aim to study growth pattern in transfusion dependent thalassaemic children.

Primary objective

To study the growth pattern in thalassaemic children of age group 2 years to 12 years who are on regular blood transfusions (2-4 weekly) and have received blood at least for one year, attending Department of Pediatrics, Assam Medical College and Hospital, Dibrugarh, Assam, India.

Secondary objective

To compare the growth pattern of the thalassaemic children who received regular blood transfusions (2-4 weekly) with those with irregular blood transfusions (>4 weekly).

METHODS

It was a cross-sectional observational study, done in Department of Pediatrics, Assam Medical College and Hospital, Dibrugarh, Assam, India from July 2014 to June 2015.

Selection of cases

Depending upon the previous year's statistics, study sample for present study was expected to be approximately 40. Author enrolled 38 cases who met the inclusion criteria.

Inclusion criteria

Thalassemic children (aged 2 years to 12 years diagnosed by high performance liquid chromatography) coming for blood transfusion and who have received blood transfusion at least for one year.

Exclusion criteria

- Thalassemic children who were suffering from systemic illness like tuberculosis, chronic renal disease, chronic liver disease and severe acute malnutrition.
- Children with sickle-thalassemia.

Ethical clearance

Necessary ethical clearance was obtained from the Institutional Ethics Committee of Assam Medical College and Hospital, Dibrugarh.

Informed verbal consent was taken from the parents/guardians of all study subjects.

History

A detailed history was taken from the patients and/or their parents regarding their presenting complaints, dietary history (24-hour recall method), age at diagnosis, number of blood transfusion in the past, interval between each blood transfusion, history of splenectomy or use of chelation therapy.

Clinical examination

A detailed general physical examination was carried out with special importance to hemolytic facies, pallor, icterus, any pigmentation of the skin. Anthropometric measurements like weight, height (length in children up to 2 years of age), BMI, Mid arm circumference (from 2 to 5 years) were taken from all patients. Weight for age, Height for age and Body Mass Index (BMI) were expressed in terms of Percentiles relative to WHO 2007 Child Growth Standards reference data.[12]

Height for age was measured from 2-12 years of age, Body Mass Index (BMI) from 2-12 years of age and Weight for age from 2-10 years of age according to WHO growth standard 2007. For children aged more than 10 years, BMI was used to assess the growth, using WHO-BMI charts 2007.[12]

Measurement of weight

Weight was measured (in kg) using a spring balance type of weighing scale. The scale was adjusted to zero before each measurement.

The subject was made to wear minimum cloths and ask to stand on the platform of the scale bare footed without touching anything and looking straight ahead. The weight was recorded to the nearest 100 grams.

Measurement of height

The height was measured for patients more than 2 years of age. Stadiometer was used to measure the height. It was taken by making the child stand against a wall, barefooted with both feet joined together and occipital region, shoulders, buttocks and heel touching the wall. Head should be in the Frankfurt's plane. The height was read to the nearest 0.1 cm.

Measurement of BMI (Body Mass Index)

The BMI was calculated for the corresponding weight (in kg) and height (in meter) using the following formula.

$$\text{BMI} = \frac{\text{Weight in Kg}}{\text{Height in m}^2}$$

Measurement of upper segment and lower segment ratio

The lower segment is measured from pubic symphysis to floor when the child is standing. Upper segment is obtained by subtracting lower segment from the height.

Measurement of mid upper arm circumference

The mid-point of left arm was marked from the bony prominence (acromion and olecranon). Then the circumference of the arm was measured using a non-stretchable plastic measuring tape. 12.5 cms-13.4 cms: borderline malnutrition, 11.5 cms-12.4 cms: mild to moderate malnutrition, <11.5 cms: severe undernutrition. (IAP guidelines)

Assessment of sexual maturity rating (SMR)

SMR was done in girls ≥10 years and in boys ≥11 years using Tanners staging scale. 1st visible sign of puberty in girls is between 8-12 years and 1st visible sign of puberty in boys is 9.5 years.[13] In boys, testicular volume of less than 6 ml at the age of 10 years is taken as puberty 'not attained'. Testicular volume is measured using Prader's orchidometer. In girls, absence of thelarche by 10 years is taken as puberty 'not attained'.

All the female patients were assessed for sexual maturity rating, in presence of a female attendant/doctor.

Systemic examination

Abdominal examination was carried out specially to look for splenomegaly and hepatomegaly. Cardiovascular examination was done to look for presence of cardiomegaly or any evidence of heart failure.

Respiratory and Central Nervous system examination was done to look for any abnormality.

Investigations

Blood Investigations done included, measurement of hemoglobin percentage, total leukocyte count, differential leukocyte count, thyroid function test and liver function test, urea, creatinine, serum ferritin. Serum ferritin was done in all the children who received more than 15 blood transfusions.

Technique of laboratory investigations

- Haemoglobin estimation: Standard acid haematin method in Heling's haemoglobinometer.
- WBC count (Total count): Neuber ruling slide after proper dilution under low power objective.
- Differential WBC count: PBS stained with Leishman's stain examined under oil immersion lens.
- Erythrocyte sedimentation rate: ESR was examined by Westergren's method and reading was taken at the end of first hour.

Estimation of serum ferritin

Serum ferritin was measured by MAG-16 kit, which is a immunoradiometric assay kit.

- Thyroid profile
- Liver function test
- Hemoglobin typing done by Bio rad D10 version of HPLC.

Statistical data analysis was done using Microsoft Excel© and SPSS software.

RESULTS

Weight for age among those regularly transfused thalassaemic children aged ≤10 years was distributed in percentiles. 4 (28.57%) out of 14 children were below <3rd percentile, 4 (28.57%) were between 3rd-15th percentiles, 6 (42.85%) were between 15th-50th percentiles. None of them had weight for age above 50th percentile (Figure 1). Height for age among those regularly transfused thalassaemic children was distributed in percentiles. 6 (27.27%) out of 22 children were below <3rd percentile, 7 (31.82%) were between 3rd-15th percentiles, 5 (22.73%) were between 15th-50th percentiles. 4 (18.18%) out of 22 had height for age above 50th percentile (Figure 2).

The BMI distribution among the regularly transfused thalassaemic children was distributed in percentiles. Majority of them, 15 (68.18%) out of 22 had BMI between 50th-85th percentiles. 6 (27.27%) out of 22 had BMI <3rd percentile. Since majority of children had height affected more than the weight, BMI is apparently normal.

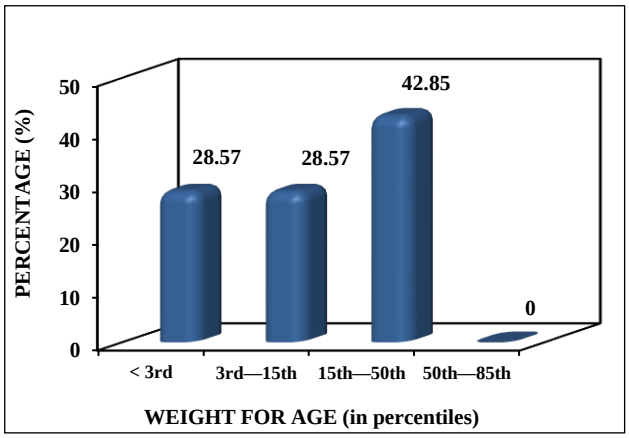

Figure 1: Distribution of weight for age in percentiles among the regularly transfused thalassaemic children aged ≤10 years.

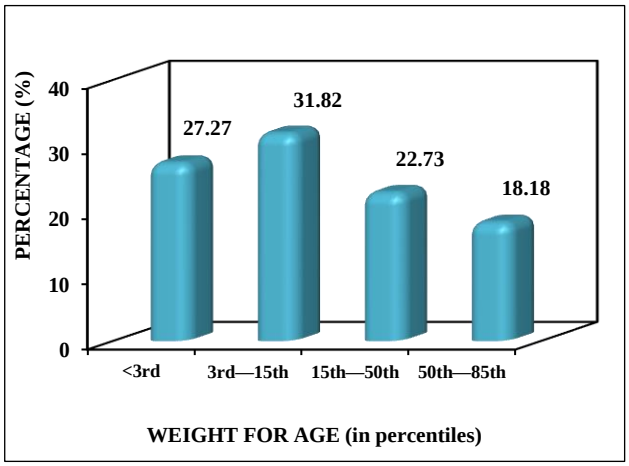

Figure 2: Distribution of height for age in percentiles among the regularly transfused thalassaemic children.

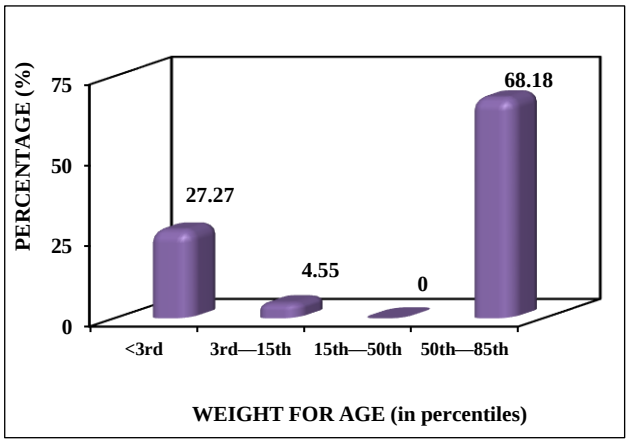

Figure 3: istribution of BMI in percentiles among the regularly transfused thalassaemic children.

Out of 8 children for whom sexual maturity rating was done, 2 (25%) had attained the puberty and 6 (75%) had

not attained the puberty yet.

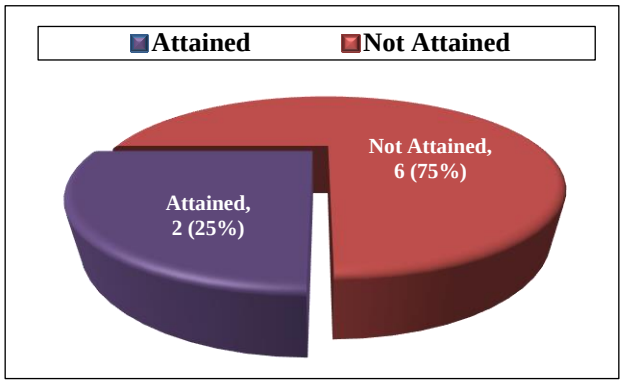

Figure 4: Distribution of attainment of puberty among the regularly transfused thalassaemic children (≥10 years in girls, ≥ 11 years in boys).

There were 4 (28.57%) out 14 regularly transfused thalassaemic children aged ≤10 years had weight for age <3rd percentile, whereas, 4(40%) out of 10 irregularly transfused thalassaemic children aged ≤10 years had weight for age <3rd percentile. Fisher's Exact test was done and p value was found to be >0.05 which was statistically not significant.

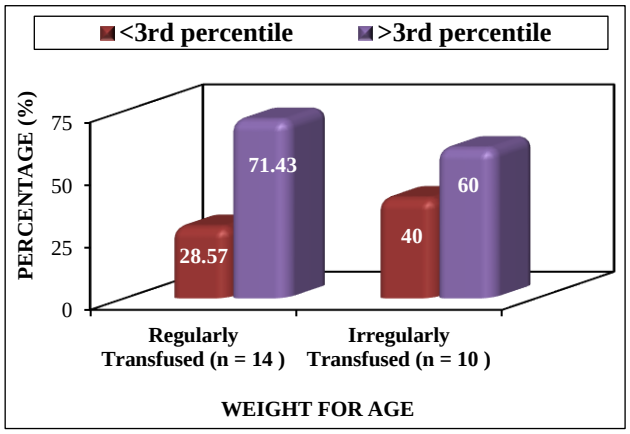

Figure 5: Comparison of weight for age among regularly and irregularly transfused thalassaemic children (aged ≤10 years).

There were 6 (27.27%) out of 22 regularly transfused thalassaemic children had height for age <3rd percentile, whereas,13 (81.25%) out of 16 irregularly transfused thalassaemic children had weight for age <3rd percentile. Chi square test was done and p-value was found to be 0.001 (P<0.05) which is highly significant.

Among regularly transfused thalassaemic children aged >10 years, 2 (25%) out of 8 had attained puberty and 6 (75%) out of 8 children had not yet attained puberty. Among irregularly transfused thalassaemic children aged >10 years, 3 (42.85%) out of 7 children had attained puberty and 4 (57.15%) out of 7 children had not yet attained the puberty. P-value is more than 0.05 which is statistically not significant.

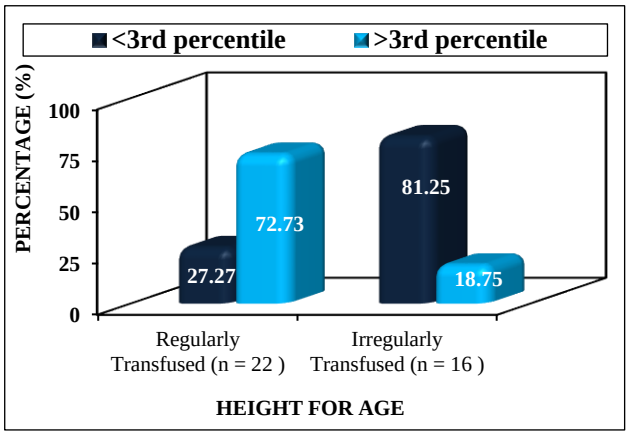

Figure 6: Comparison of height for age among regularly and irregularly transfused thalassaemic children.

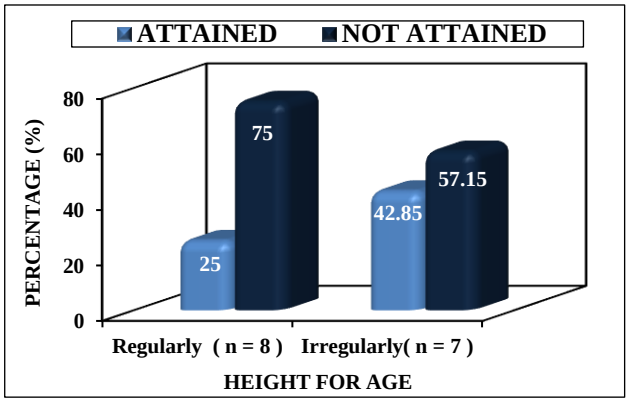

Figure 7: Comparison of attainment of puberty in regularly and irregularly transfused thalassaemic children (≥10 years in girls, ≥ 11 years in boys).

Upper segment: Lower segment ratio was distributed among all the thalassaemic children enrolled for the study according their age. US: LS ratio was 1.1:1.0 between age group 2-4 years, 1.07:1.0 between 4.1-7 years age group, 1.02:1.0 between 7.1-10 years age group and 1.12:1.0 between 10.1-12 years age group. Mean US:LS RATIO in our study was US:61.11±11.53 cms and LS: 56.18±11.61 cms.

Table 1: Distribution of mean upper segment: lower segment (US:LS) ratio among all thalassaemic children.

Age (in years)	Mean US : LS ratio
2-4	1.1: 1.0
4.1-7	1.07: 1.0
7.1-10	1.02: 1.0
10.1-12	1.12: 1.0
Mean±SD	US: 61.11±11.53 LS: 56.18±11.61

DISCUSSION

Distribution of weight for age

In the present study, among the regularly transfused thalassaemic children 28.57% children had weight for age <3rd percentile as per WHO standards. Among the irregularly transfused thalassaemic children, 40% children had weight for age less than 3rd percentile.

Gomber S et al, observed that 30.8% of subjects had a weight less than 3rd percentile.[14] Pemde HK et al, observed that 13.3 % of the subjects had weight for age less than 3rd percentile.[15] Singhal et al, in their study observed that 76.31% thalassaemic males and 72% thalassaemic females had weight less than 5th percentile.[16] Hashemi A et al, observed 45.71% had weight less than 5th percentile.[17] Nazar Baker et al, observed 61% of subjects had underweight.[18]

Our study correlated well with the Gomber S et al, and Pemde HK et al, studies. From our study it is seen that irregularly transfused thalassaemic children are affected more than the regularly transfused children though it was statistically not significant (p >0.05).

Distribution of height for age

In the present study, among the regularly transfused thalassaemic children 27.27% had height for age less than 3rd percentile and among the irregularly transfused thalassaemic children 81.25% had height for age less than 3rd percentile based upon the WHO standard.

Singhal et al, in their study observed that height parameters of studied subjects when compared with NCHS standards showed that 55.26% thalassaemic males and 52% thalassaemic females were found to have short stature.[16] Pemde HK et al, found that 33.11% of the study patients had short stature. Gomber S et al observed that 75% of subjects had standing height below 3rd percentile.[14] Hashemi A et al, observed 65.71% of patients had height less than 5th percentile.[17]

Yesillipek MA et al, observed that 32.45% of the study subjects had height for age less than 3rd percentile.[19] Our study correlated well with the Gomber S et al, and Hashemi A et al, showing stunting is a serious problem in the transfusion dependent thalassaemic children.[14,17]

From our study it is shown that thalassaemic children are stunted but stunting is more seen in irregularly transfused thalassaemic children which is statistically highly significant (P=0.001).

Distribution of BMI

In the present study, majority of children, 68.18% had normal BMI and 27.27% had BMI less than 3rd percentile. Pemde HK et al, observed that 24.19 % of the study subjects had BMI less than 3rd percentile.[15]

High percentage of normal BMI is seen mainly because most of the children had stunting that is height is more affected than the weight. This was statistically not significant (P >0.05).

Attainment of puberty

In the present study, among the regularly transfused thalassaemic children (≥10 years in girls, ≥11 years in boys) 25% have attained the puberty, 75.5% have not attained puberty yet. Among the irregularly transfused thalassaemic children 42.85% have attained puberty and 57.15% have not attained puberty yet.

Both the group of children had high number of cases with pubertal changes not yet attained, however this is statistically not significant (P >0.05). Nazar Baker et al, observed that 97.5% had delayed puberty.[18] Anita saxena et al, observed in their study, delayed pubertal spurt at the age of 16 yrs in boys and 15 years in girls.[20] Yesillipek MA observed 74.5% of the study subjects had delayed puberty.[19]

Upper segment: lower segment ratio (US:LS)

In this study, the mean US was 61.11±11.53 cms and mean LS was found out to be 56.18±11.61 cms. From our study we observed that the US:LS ratio is affected in the younger age group (2-4 years) with the mean ratio being 1.1:1.0. Upper trunk length is affected more in the younger age group.

CONCLUSION

Among the regularly transfused thalassaemic children both weight and height are affected almost to the same extent. Among the irregularly transfused thalassaemic children height is severely affected than weight. Compared to regularly transfused thalassaemic children, irregularly transfused children are more stunted.

Pubertal growth spurt is delayed in transfusion dependent thalassaemic children irrespective of the regularity of the transfusion. Pubertal growth spurt is delayed more in regularly transfused children then irregularly transfused children, probably due to, iron overload suppressing the hypothalamo-pituitary-gonadal axis, to be the cause.

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