



## ENDOCRINOPATHIES IN THALASSEMIA WITH SPECIAL REFERENCE TO ANTHROPOMETRY

**Dr. Chirag Shah**

MD (Pediatric), Associate Professor, Pediatric Department B.J. Medical College, Civil Hospital Campus, Ahmedabad, Gujarat, India

**Dr. Priyanka Makwana**

MD (Pediatric), Assistant Professor, Pediatric Department Narendra Modi Medical College, Ahmedabad, Gujarat, India

**Dr. Jatin Jadav**

M.Ch (Pediatric Surgeon), Assistant Professor, General Surgery Department Dr. M.K. Shah Medical College And Research Center Ahmedabad, Gujarat, India

### ABSTRACT

**Background:** Despite intensive iron chelation therapy, growth retardation, hypo gonadotropic hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, osteopenia and osteoporosis represent the common endocrinopathies in pediatric thalassemia patients. **Purpose:** To study profile of blood transfusion, chelation therapy and complications in thalassemia children, to study anthropometric measurements, to study the incidence of growth retardation & endocrine complications in thalassemia patients. **Methods:** This observational -prospective study is carried out among children in thalassemia clinic. The detailed history regarding blood transfusion and use of iron chelator taken and various anthropometric measurements recorded. Blood and radio-graphical investigations are done at blood transfusion date or on follow up. **Results:** Mean duration of blood transfusion was less than 2 week in 31.1%, between 2-4 week in 46.7% and more than 4 week in 22.2%. In present study, height less than 3rd percentile observed in 53.6% male and 64.7% female and between 3rd -50th percentile in 37.1% male and 23.4% female. Weight less than 3rd percentile seen in 32.2% male and 29.4% female while 3rd -50th percentile was observed in 42.8% male and 47% female. **Conclusion:** Growth retardation was observed in 29.6% of children in present study. Juvenile Diabetes & Hypothyroidism was seen in 2.2% & 1.5% respectively.

**KEYWORDS :** Endocrine, thalassemia, anthropometry, growth retardation, children

#### Inclusion Criteria

- Patients coming for regular blood transfusion at thalassemia clinic and age group between 6 to 12 years of age.
- Our aim of study was to find out the magnitude of growth retardation & endocrine complications which are commonly seen in older children as disease become chronic and iron overload related endocrinopathies also develops after reasonable number of blood transfusion during early and mid-childhood.

#### Exclusion Criteria

- Age group <6 years of age and >13 years of age.
- All systemic disorder affecting growth such as genetic, cardiac, renal were excluded.
- Other haemoglobinopathies excluded.
- Outdoor patients excluded.
- Patients that have lost follow up not included.

Study period is 1/10/2017 to 1/10/2019.

This observational -prospective study is carried out among children in thalassemia clinic in civil hospital receiving regular blood transfusion. The detailed history regarding blood transfusion and use of iron chelation taken and various anthropometric measurements taken on standardized stadiometer and weight machine. Growth data plotted on WHO adjusted chart. A child is considered short if height is below 3<sup>rd</sup> percentile. Patient's body mass index also calculated. Classification of nutritional status done according to (Body mass index) BMI <13: Severe under-nutrition, BMI 13-15: Moderate under-nutrition, Normal: 15-22 and Overweight: >22. Pubertal status is evaluated according to tanner stages. Complete blood count is done at the time of visit for blood transfusion. While renal, liver function test, serum ferritin level done every 3 monthly. Mean hemoglobin level and mean serum ferritin level is calculated. Thyroid function test, serum calcium levels are done every 6 monthly. Random blood sugar, Hb1ac level as and when required. Radiographical investigations like ultrasound, 2D echo also done. Detailed information of collected data entered in proforma and data will be summarized in form of tables and conclusions drawn accordingly.

- Out of 135 patients, growth retardation observed in 29.6% & endocrine complication observed in 3.7% children. Chhabra et al in their study of 114 Thalassemia children of age group 8-16 years reported underweight in 78.1% & short stature in 56.1%.

Vasundhara Kumari et al in her study of 74 Thalassemia children of the age group of 3-10 years, observed grade 2 & 3 grade malnutrition in 70%.

Relatively lower incidence of endocrine complications in the present study could be because the study population was up to 12 years of age only whereas common endocrinopathies are more seen in the late adolescent age & in second decades. National guidelines for management of Thalassemia by Anupam Sachdeva 1<sup>st</sup> edition 2014 also mentioned that endocrine morbidities occur after 10 years of age.

- In the age group of 6-9 years 26.9% (17 out of 63) and in the age group of 10-12 years 31.9% (23 out of 72) developed growth retardation.

Similarly, in the age group of 6-9 years 3.1% (2 out of 63) and in the age group of 10-12 years 4.1% (3 out of 72) developed endocrine complication.

Dr. Mukesh Kumar Sharma et al observed 57.7% of growth retardation & other endocrine complications in study of 84 Thalassemia children of 3-9 years age group.

No statically significant difference was observed between two age group with respect to growth retardation (P value=0.3965) & endocrine complication (P value=0.0927) as the P value is < 0.05 in both.

- Male: Female ratio was 1.6: 1 in the study population (45).

Out of 87 male children 25 (28.7%) developed growth retardation and 3 (3.4%) developed endocrine complications. Out of 48 female children 15 (31.2%) developed growth

retardation and 2 (4.1%) developed endocrine complications. Chhabra et al reported Male: Female ratio of 1.2:1. Vasundhara Kumari et al observed Male: Female ratio of 3.3:1.

No statically difference observed between both sex with respect to growth retardation (P value=0.75941) and endocrine complication (P value=0.8324) as the P value is < 0.05 in both.

- 48.8% of children were in the age group of 6 months to 2 years when they were diagnosed for the first time.
- There was family history of Thalassemia major in 32 siblings. Similarly, history of Thalassemia minor in single & both parents was seen in 14 & 27 respectively.

Total 19 siblings were found to be Thalassemia minor. There was carrier form of Hb S and Hb E in one parent each.

- Mean duration of blood transfusion was less than 2 week in 31.1%, between 2-4 week in 46.7% and more than 4 week in 22.2%.
- Annual blood requirement was <250ml/kg/year in 68.8% and it exceeds more than 250 ml/kg/year in remaining 31.1%.

**Mean Ferritin Level:**

Mean Serum ferritin Level(ng/dl)	Number (45)	Vasundhara et al,2012(n=74)(1)
<1000	2(4.4%)	13(17.5%)
1000-2000	19(42.2%)	30(40.5%)
>2000	24(53.3%)	31(41.9%)

- 53.3% of the Thalassemia children were having mean serum ferritin level between >2000ng/dl. In spite of the regular iron chelation, ferritin level less than 1000ng/dl was maintained in only 4.4%.

We are not able to explain high ferritin level in most of these children but poor compliance & inter-current biochemical alteration (LFT, RFT etc.) leading to transient discontinuation may lead to this.

**Pre-transfusion Mean Hemoglobin Level:**

Pre-transfusion Mean Hb	Present study (45)	Vasundhara Kumari et al,2012(1)
<7	12(26.6%)	23(31.1%)
7-10	25(55.6%)	44(59.4%)
>10	8(17.8%)	07(9.4%)

- In present study 25 (55.6%) Thalassemia children were having mean pre transfusion hemoglobin level between 7-10gm/dl.

Vasundhara Kumari et al<sup>(1)</sup> also reported pre transfusion Hemoglobin level of 7-10gm/dl in 59.4% in their study.

The study center is following moderate transfusion regimen with target to maintain pre transfusion hemoglobin in the range of 9- 11gm/dl. In spite of following moderate transfusion regimen low pre transfusion hemoglobin in significant number of the children in the study group may explain the reason of growth retardation.

To maintain the growth velocity, it is desirable to keep pre transfusion hemoglobin more than 10gm/dl.<sup>(2)</sup>

- 57.5% of these children receiving Deferasirox in the dose range of 20-35 mg/kg/day whereas remaining 42.3 % were on 35-45mg/kg/day.

**Anthropometric Measurement:**

Measure-ment	Sex	Growth retardation		
		<3rd percentile	3rd-50th percentile	> 50th Percentile
Height	Male (N=28)	15(53.6)	10(37.1)	3(10.7)

	Female (N=17)	11(64.7)	4(23.4)	2(11.7)
	Total (N=45)	26(57.8)	14(31.1)	5(11.1)
Weight	Male (N=28)	9(32.2)	12(42.8)	7(25)
	Female (N=17)	5(29.4)	8(47)	4(23.6)
	Total (N=45)	14(31.1)	20(44.4)	11(24.4)

In present study, height less than 3<sup>rd</sup> percentile observed in 53.6% male and 64.7% female and between 3<sup>rd</sup> -50<sup>th</sup> percentile in 37.1% male and 23.4% female.

Weight less than 3<sup>rd</sup> percentile was seen in 32.2% male and 29.4% female while 3<sup>rd</sup> -50<sup>th</sup> percentile was observed in 42.8% male and 47% female.

Vasundhara et al study shows height <3<sup>rd</sup> percentile in 60.8% and between 3<sup>rd</sup> to 50<sup>th</sup> percentile in 35.1%. Similarly Vasundhara et al study shows weight below 3<sup>rd</sup> percentile in 73% and between 3<sup>rd</sup> to 50<sup>th</sup> percentile in 24.2%.

- In male moderate under-nutrition was observed in 50% (14 out of 28) whereas severe under-nutrition was seen in 17.8% (5 out of 28). Similarly, moderate & severe under-nutrition was seen in 41.1% & 29.4% of females.
- Significant growth retardation in Thalassemia children is due to multiple reasons like chronic hypoxia, intercurrent infections, increased BMR, drug related arthropathy & endocrine disturbances.
- There was no child with delayed puberty in either sex. As the study population was less than 12 years of age, we could not derive any conclusion with respect to velocity of puberty.

Chhabra et al<sup>(3)</sup> has observed delayed puberty in 86.9% Thalassemia children of age group between 8-16 years.

First sign of onset of puberty and the hallmark of SMR (sexual maturity rating) 2 in boys is testicular enlargement begins as early as 9 and ½ years.

Similarly, the first sign of onset of puberty and hallmark of SMR 2 in females is the appearance of breast bud usually between 8 to 12 years of age.

Puberty is considered as delayed as respective signs of SMR stage 2 do not appear by 13 years in female and 14 years in males.

- Growth retardation was observed in 29.6% of children in present study. Juvenile Diabetes & Hypothyroidism was seen in 2.2% & 1.5% respectively.

Dr Mukesh Sharma et al reported growth retardation – short stature in 16.3%. He also observed endocrinopathies in form of Juvenile Diabetes in 4%, Hypothyroidism in 11.4% and delayed puberty seen in 6.52%.

**Endocrine Complications:**

Complica-tions	Present study		Dr Mukesh Kumar et al (4) Age group 3-17 years. (N=84)	D Sanctis V PER,2004,2, 279 (N=3817) (5)	
	Total Number (135)	Percentage (%)		MALE	FE-MALE
Growth retardation	40	29.6%	16.3%*	31.1%*	30.5%*
Growth hormone Deficiency	-	-	-	7.9%	8.8%

Diabetes mellitus	3	2.2%	4%	9.9%
Hypothyroidism	2	1.5%	11.4%	3.2%
Hypoparathyroidism	-	-	-	6.9%
Delayed puberty	-	-	6.52%	40.50%
Osteopenia and Osteoporosis	-	-	19.5%	

In large multi-centric study of 3817 thalassemia children from 29 countries De Sanctis et al reported short stature in 31.1% male and 30.5% female. Similarly, Growth hormone deficiency was reported in 7.9% in males and 8.8% amongst females. Amongst the various Endocrine complications delayed puberty was in 40.5% followed by Diabetes Mellitus in 9.9%, Hypoparathyroidism in 6.9% and Hypothyroidism in 3.2%.

We could not confirm the Growth Hormone deficiency in our study because of cost factor & non availability of diagnostic facility at the study center.

Relatively lower incidence of Endocrine complications in the present study could be because the study covered population up to 12 years of age, whereas Endocrinopathies are more commonly seen in the late adolescent age & in second decades.

- 6 patients having transfusion transmitted infection (one Hepatitis B & 5 Hepatitis C).
- All patients received nutritional supplement (multivitamin, calcium, folic acid, zinc) as routine therapy.

Children with endocrinopathies were treated with hormone therapy. Three patients of diabetes mellitus with Insulin and two patient of hypothyroidism with Thyroxin.

Special vaccine against capsulated organism was given to one thalassemia child who was subjected for splenectomy.

**CONCLUSION**

- In the present study out of 135 Thalassemia children, Growth retardation was observed 29.6% and Endocrine complications was seen in 3.7%.
- Growth retardation was present in 26.9% and 31.9% of children in the age group of 6-9 years & 10-12 years respectively. Endocrine complications were seen in 3.1% & 4.1% of children in the age group of 6-9 years & 10-12 years respectively.
- Out of 87 male children 28.7% & out of 48 females, 31.2% developed growth retardation. Similarly, 3.4% of males & 4.1% of females developed endocrine complications.
- 48.8% of patients were diagnosed between 6 months to 2 year of age.
- Family history of Thalassemia minor in single & both parents was seen in 14 & 27 respectively. Total 19 siblings were found to be thalassemia minor. Carrier of HbS and HbE was also observed in one parent each.
- Mean duration of blood transfusion was less than 2 weeks in 31.1%, between 2-4 week in 46.7% and more than 4 weeks in 22.2%.
- Annual PCV (packed cell volume) requirement was <250ml/kg/year in 68.8% and it exceeds more than 250 ml/kg/year in remaining 31.1%.
- 53.3% of the Thalassemia children were having mean serum ferritin level between >2000ng/dl. In spite of regular iron chelation ferritin level less than 1000ng/dl was maintained in only 4.4%.
- In 55.6% of children mean pre transfusion hemoglobin level was between 7-10gm/dl. To maintain the growth

velocity, it is desirable to keep pre transfusion hemoglobin more than 10gm/dl.

- 57.5% of the children receiving Deferasirox in the dose of 20-35 mg/kg/day whereas remaining 42.3 % were on 35-45mg/kg/day.
- In 53.6% male and 64.7% female, height was below 3<sup>rd</sup> percentile, similarly, in 32.2% male and 29.4% female, weight was less than 3<sup>rd</sup> percentile. (According to WHO Standard.)
- According to BMI (body mass index) moderate under-nutrition was observed in 50% of males and 41.1% of females. Severe under-nutrition was seen in 17.8% of male and 29.4% of female.
- In the age group of 10-12 years, 60% male and 54.5% female were having SMR stage 1. Whereas 40% male and 45.4% female developed SMR stage 2. As the study population was less than 12 years of age, we could not derive any conclusion with respect to velocity of puberty.
- Growth retardation was observed in 29.6% of children in present study. Juvenile Diabetes & Hypothyroidism was observed in 2.2% & 1.5% respectively.
- Chronic Hepatitis B (one) and Chronic Hepatitis C (five) were the most significant co-morbid condition acquired following repeated blood transfusion.
- Three patients were treated with insulin and two patients with thyroxin. One patient was subjected for splenectomy following hypersplenism.

**REFERENCES**

1. Vasundhara Kumari et al growth retardation and malnutrition in children with thalassemia, Indian J. prev. Soc. Med. Vol. 43 No. 2, 2012
2. Cappellini M, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. guidelines for clinical management for thalassemia; 2<sup>nd</sup> revised edition; Endocrine complication in thalassemia major. 2008; pp 64-9.
3. Chhabra GS, Sodhi MK. Patterns of growth retardation and sexual maturation in children having beta thalassemia. J Nepal pediatric soc 2016;36(1):56-60
4. DR Mukesh Kumar Sharma et al international journal of science and research.
5. De sanctis V, Soliman AT, Eleftheriou A, Malaventura C; Thalassemia International Federation Study on Growth and Endocrine Complications in thalassemia. Prevalence of endocrine complications and short stature in patients with thalassemia major: a multicenter study by thalassemia International Federation (TIF). *Pediatr Endocrinol Rev* 2004;2: 249-55.