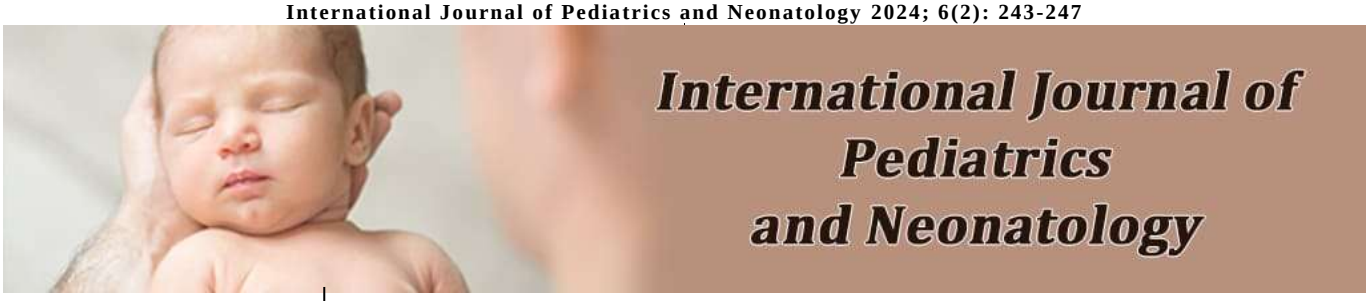

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A study of growth, puberty and endocrine functions in children with beta thalassemia major in a tertiary care hospital of south Rajasthan

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Abstract
Aim: Endocrinopathies are common in patients with thalassemia major (TM) and affect their quality of life. Our aim was to evaluate the frequency of growth retardation and endocrine complications in these patients.
Materials and Methods: 226 patients aged 3-18 years with Thalassemia Major were evaluated for height, weight, body mass index (BMI), and pubertal stage. Blood tests for endocrine function, and tanner staging for pubertal development were done.
Results: Out of 226 children of beta thalassemia major, males were 51.3% (116) and females were 48.7% (110). There was no significant gender difference in thalessemia patients in our study. The mean BMI was 16.61 kg/m^2 with SD 5.34 and 16.26 kg/m^2 with SD 2.91 for age group of 5-10 years and 11-18 years respectively. BMI of both the age group was almost similar showing increased incidence of under nutrition as the disease and its complication evolutes. There was significant growth delay present in thalassemia patient (p value <0.0001 using Chi Square test with CI: 55.14%-72.95%).
Conclusion: Endocrine disorders are very common among multi-transfused beta thalassemia major patients which unfortunately are not detected on time in resource limited countries like India. Ferritin concentrations are not a reliable and sensitive predictor of these complications. In the current study, there was significant growth delay present in the patients suffering from Beta thalassemia. Growth delay not only causes a physical constraint on a children but also effects their psychological wellbeing. Early detection of growth and endocrine abnormalities not only will improve the overall health of the patients but will also reduce the economic burden of chronic illness on the family.

Keywords: Thalassemia, growth and puberty, endocrinopathies

Introduction
Thalassemia is the most common genetic blood disease, and patients with thalassemia major (TM) require regular blood transfusions [1]. With more intense blood transfusion and administration of adequate chelation therapy, the life expectancy has increased [2]. Although the main cause of death in TM is cardiac failure, endocrine complications are the most important problems affecting the quality of life in these patients [2, 3] Early chelating therapy started at 5-6 years of age, prior to the onset of adrenarche and before extremely high ferritin levels are reached, may allow for a normal onset of puberty and sexual maturation [4]. The aim of the study was to evaluate the growth and pubertal development in thalassemic patients.

Methodology
An observational cross sectional study was done in a tertiary care hospital of south Rajasthan over a period of 6 months from January 2022 to June 2022. 226 children with Beta thalassemia major were included in the study after taking consent from the parents. All participants signed an informed consent form at enrolment. Patients were excluded if they were unwilling or unable to participate in the study, or if they were diagnosed with comorbid conditions, potentially affecting their participation in the study. Clinical and laboratory data were collected by review of medical records. Socioeconomic data were collected by parent's interview. A detailed physical examination was done and clinical history including the frequency and age of starting of blood transfusion and chelation therapy were taken.

Detailed family history was obtained including three-generation pedigree analysis, parental consanguinity, and number of similarly affected family members.

Anthropometric measures including weight, height and body mass index were recorded and expressed as standard deviation scores. Mid- parental height (MPH) adjusted for sex was used as Target height and expressed as standard deviation scores. Short stature was defined as height less than -2SD below the mean for respective age or height less than 3 percentile for respective age. Bone age was calculated with the help of wrist and elbow x-rays in children with short stature to determine the ratio of bone age and chronological age according to the Greulich and Pyle atlas [2] Body mass index (BMI) was recorded using the formula weight (kg)/[height (m^2)] to evaluate for nutritional status of these children.

Sexual maturation was determined using Tanner [6] staging of puberty after taking parental consent to look for delayed puberty. Onset of menarche and breast development were recorded. Delayed puberty was defined as failure to achieve secondary sexual characteristics by the age of 12 years in girls and 14 years in boys.

Investigations such as Thyroid profile including free T_3, T_4 and TSH, fasting blood glucose, HbA1C, serum ferritin, serum electrolytes, serum calcium and phosphorus, serum alkaline phosphatase, vitamin D3 level, PTH were done to determine any endocrine abnormality in children.

All the numerical and categorical data was recorded and statistical analysis was done using the chi-square test. A p-value less than 0.05 was considered significant.

Results

Table 1: Socio-demographic features of Thalassemia Patients

S. No	Socio-demographic factors	Total (%)
1	**Gender**	
	Males	116 (51.3%)
	Female	110 (48.7%)
2	**Age**	
	5-10 years	88 (38.9%)
	11-18 years	138 (61.1%)
3	**Religion**	
	Hindu	180 (79.6%)
	Muslim	32 (14.2%)
	Others	14 (6.2%)
4	**Socio-economic status (Kuppuswamy scale 2022)**	
	I	4 (1.8%)
	II	62 (27.5%)
	III	102 (45.3%)
	IV	45 (19.9%)
	V	10 (4.5%)

In this study, males were 51.3% (116) and females were 48.7% (110). According to age wise distribution, 38.9% children were in age group 5-10 years; 61.1% children were in age group 11-18 years. Maximum no of patients enrolled were Hindu (79.6%) followed by Muslim (14.2%). Other community were 6.2%. As per Modified Kuppuswamy scale, 1.8% of enrolled patient belonged to class I, 27.5% were in group II, 45.3% were in class III, 19.9% were in class IV and 4.5% were in socio economic class V. [Table 1].

Table 2: Socio-demographic Pattern in Thalassemia Patients

S. No	Socio demographic factors	Total (%)	p value
1	**Gender**		
	Males	116 (51.3%)	0.5664
	Female	110 (48.7%)	
2	**Age**		
	5-10 years	88 (38.9%)	< 0.0001
	11-18 years	138 (61.1%)	
3	**Religion**		
	Hindu	180(79.6%)	< 0.0001
	Muslim	32(14.2%)	
	Others	14 (6.2%)	

In the present study, the case load of thalassemia was significantly present in age group of 11-18 years. Also it was significantly present in Hindu community than in other community (p value <0.0001) [Table 2]

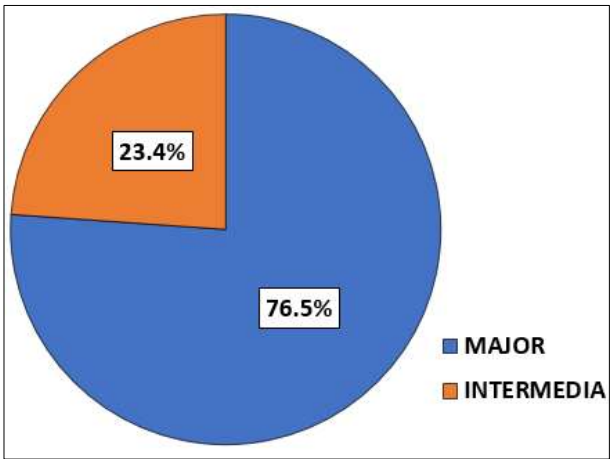

Fig 1: Distribution of Thalassemia types

76.5% children attending to thalassemia clinic in this study were Thalassemia Major. Only 23.4% were thalassemia intermedia. [Figure 1]

Table 3: Anthropometric measurement of Thalassemia patient

S. No	Character	MEAN	SD
1	**Weight for age**		
	5-10 years	18.3 kgs	4.1
	11-18 years	31.9 kgs	8.9
2	**Height for age**		
	5-10 years	106.9 cm	11.8
	11-18 years	139.3	14.4
3	**BMI**		
	5-10 years	16.61 kg/m^2	5.34
	11-18 years	16.26 kg/m^2	2.91

In the present study, the mean weight for age for 5-10 years age group was 18.3 kg with SD of 4.1. For the age group 11-18 years, the mean weight for age was 31.9 kg with SD of 8.9.

In regards to height for age, the mean height for age for 5-10 years was 106.9 cm with SD of 11.8. The mean height for age for 11-18 years was 139.3 cm with SD of 14.4.

BMI of both the age group was almost similar showing increased incidence of under nutrition as the disease and its complication evolutes. The mean BMI was 16.61 kg/m^2 with SD 5.34 and 16.26 kg/m^2 with SD 2.91 for age group of 5-10 years and 11-18 years respectively. [Table 3]

Table 4: Laboratory Investigations of Beta thalassemia patients

S. No	Variant	Mean	SD
1	Hemoglobin (g/dl)	7.07	1.46
2	WBC (x 10^9 /L)	8893	3173
3	Platelet (cumm^3)	342879	166288
4	Bilirubin (mg/dl)	1.59	0.6
5	SGPT (iu/l)	95	37.8
6	SGOT (iu/l)	60	59.6
7	UREA (mg/dl)	23	10.4
8	Creatinine (mg/dl)	0.45	0.23
9	Random Blood Glucose (g/dl)	98	26.5
10	calcium (mg/dl)	8.4	0.61
11	Alkaline phosphatase (u/l)	214	81.9
12	phosphorous (mg/dl)	5.07	0.89

In the present study, the mean hemoglobin was 7.07 g/dl with SD of 1.46. Total blood count done had a mean of 8893 X 109 /L with SD of 3173.The mean platelet level was 3,42,879 cumm3. Liver function test showed elevated mean bilirubin of 1.59 mg/dl with SD of 0.6, SGPT was 95 IU/L with SD of 37.8; SGOT was 60 IU/L with SD of 59.6. The kidney function test, random blood glucose, calcium level were normal. The alkaline phosphatase had a mean of 214 U/L with SD of 81.9. The mean phosphorous level was 5.07 mg/dl with SD of 0.89. [Table 4]

Table 5: Growth and Endocrine complications of beta Thalassemia patients

S. No	Systems involved	Parameters	Absent	Present	p value	CI
1	Endocrinology	**Delay growth**			<0.0001	55.14%-72.95%
		Osteoporosis	24 (17.3%)	114 (82.6%)		77.50%-92.05%
		5-10 year	88 (93.6%)	6 (6.4%)		12.83%-35.41%
		11-18 year	86 (62.3%)	52 (37.7%)		87.88%-95.12%
		Overt Hypothyroidism	219 (96.3%)	7 (3.7%)		62.19%-75.38%
		Subclinical Hypothyroidism	199 (81.8%)	27 (12.2%)		
2	Allergy	**Transfusion related anaphylaxis**				82.96%-91.75%
		Chelation related	213 (94.2%)	13 (5.8%)		79.75%-89.42%
		anaphylaxis	210 (92.8%)	16 (7.2%)		
3	Gastroenterology	Elevated transaminase	174 (79%)	52 (21%)		49.83%-64.79%
		Bile stones	222 (98.2%)	4 (0.8%)		93.89%-98.64%
		Elevated creatinine	212 (93.8%)	14 (6.2%)		82.03%-91.09%
4	Infectious	Hepatitis B	224 (99.1%)	2 (0.9%)		94.96%-99.11%
		HIV	225 (99.6%)	1 (0.4%)		96.38%-99.67%
5	Others	Thrombo-embolic events	225 (99.6%)	1 (0.4%)		96.38%-99.67%

In the present study, there was significant growth delay present in thalassemia patient (p value <0.0001 using Chi Square test with CI: 55.14%-72.95%). No significant difference was found in patients with thalassemia in terms of osteoporosis, hypothyroidism, transfusion and Chelation related anaphylaxis, elevated liver enzymes, elevated creatinine level, increased incidence of bile stones. There were no significant differences in thalassemia patient in terms of Hepatitis B, HIV infection or thrombo-embolic events in this current study. [Table 5]

Discussion

In a study done by Belma Haliloglu [1], out of 62 patients of Beta Thalassemia Major, 53.2% (33) were females and 46.7% (29) were males [1]. A similar study done by Ayhan Yaman [7] in Turkey, showed 56.7% (38) males and 44.3% (29) females, out of 67 patients enrolled in the study [7]. In a study done by A. Mehrvar [10], out of 437 patients enrolled, 43.9% were females and 56.1% were males [10] A study done Bushra Moiz [11] by showed 196 males and 171 females, out of 367 patients enrolled [11] In this study, out of 226 children of beta thalassemia major, males were 51.3% (116) and females were 48.7% (110). There was no significant gender difference in thalessemia patients in our study. In a study done by Belma Haliloglu [1], the mean age of thalassemic patients were 10.4+- 1.31 years [1] A similar study done by Ayhan Yaman [7] in Turkey, showed the mean age of 10.3 +- 4.8 years [7] In the study done by Ayca Altincik [9], the mean age was 12.39 +- 3.72 years [9] In this study, the mean age of thalassemic children were 10.2 +- 3.8 years. According to age wise distribution, 38.9% children were in age group 5-10 years; 61.1% children were in age group 11-18 years.

Ayhan Yaman [7] did a study in Turkey, which showed 90.32% (56) patients were of Thalassemia Major and 17.7% (11) patients were of Thalassemia Intermedia out of 67 patients enrolled [7] In a study by A. Mehrvar [10], 86.7% (369) patients were Thalessemia Major and 13.3% (58) were of Thalessemia Intermedia, out of 437 patients enrolled [10] In this present study (173) 76.5% children attending to thalassemia clinic were Thalassemia Major and only (53) 23.4% were thalassemia intermedia.

In the study done by Amita Moirangthem [13], out of 217 thalessemia patients enrolled in study, according to modified kuppuswamy scale, 5.2% belonged to Class I (upper class), 28.3% to Class II (Upper Middle), 41% to Class III (Lower Middle), 24%to Class IV (Upper Lower) and 1.4% to Class V (Lower) [13] A similar study done by Rajnish Singh [14] showed the socioeconomic distribution as 8.6% patients belonging to Class I, 18.1% to Class II, 46.7% to Class III, 21% to Class IV and 5.7% to Class V, out of thalessemia patients enrolled. The religion wise distribution showed

53.3% were Hindu, 10.5% were Muslim and 35% were others [14]. In a study done by Srinivas PV [15], out of patients, none of them belonged to Class I, 4.6% to Class II, 21.5% to Class III, 56.9% to Class IV, and 16.9% to Class V [15]. In our study, maximum no of patients enrolled were Hindu (79.6%) followed by Muslim (14.2%). Other community were 6.2%. As per Modified Kuppuswamy scale, 1.8% of enrolled patient belonged to class I, 27.5% were in group II, 45.3% were in class III, 19.9% were in class IV and 4.5% were in socio economic class V.

In the study done Belma Haliloglu [1], Mean height was -1.63 +- 1.26 and mean weight was 1.44 +- 1.31 and mean BMI was 0.7+- 1.07. The frequency of < -2SD was 37% for height, 34% for weight and 11% for BMI. Short stature and low BMI were more prevalent in more than 7 years of age [1]. In the study done by Ayhan Yaman [7] mean height was -2.86 +- 1.51 [7]. A study done by Yesim Aydinok [8] showed the presence of short stature in (15) 40%, out of 37 patients enrolled which were less than 18 years of age [8]. In a study done by Ayca Altincik [9], short stature was present in 40% (10 females and 9 males) out of 45 patients enrolled and the mean age was 12.39 +- 3.72 years [9]. In this present study, the mean weight for 5-10 years age group was 18.3 kg with SD of 4.1. For the age group 11-18 years, the mean weight for age was 31.9 kg with SD of 8.9. In regards to height for age, the mean height for age group for 5-10 years was 106.9 cm with SD of 11.8. The mean height for age group 11-18 years was 139.3 cm with SD of 14.4. The mean BMI was 16.61 kg/m2 with SD 5.34 and 16.26 kg/m2 with SD 2.91 for age group of 5-10 years and 11-18 years respectively. BMI of both the age group was almost similar showing increased incidence of under nutrition as the disease and its complication evolutes.

In a study done by Ayca Altincik [9], the mean pre-transfusion hemoglobin of thalessemia patients was 8.8 +-0.8 g/dl and mean calcium was 9.4 +- 0.46 [9]. In the present study, the mean hemoglobin was 7.07 g/dl with SD of 1.46. Total blood count done had a mean of 8893 X 109 /L with SD of 3173. The mean platelet level was 3,42879 mm^3. Liver function test showed elevated mean bilirubin of 1.59 mg/dl with SD of 0.6, SGPT was 95 IU/L with SD of 37.8; SGOT was 60 IU/L with SD of 59.6.The kidney function test, random blood glucose, calcium level were normal. The alkaline phosphatase had a mean of 214 U/L with SD of 81.9. The mean phosphorous level was 5.07 mg/dl with SD of 0.89.

A study done by Ayca Altincik [9], showed pubertal delay in 25% in both males and females out of 45 patients enrolled.[9] In the present study, there was significant growth delay present in thalassemia patient (p value <0.0001 using Chi Square test with CI: 55.14%-72.95%). No significant difference was found in patients with thalassemia in terms of osteoporosis, hypothyroidism, transfusion and Chelation related anaphylaxis, elevated liver enzymes, elevated creatinine level, increased incidence of bile stones. There were no significant differences in thalassemia patient in terms of Hepatitis B, HIV infection or thrombo-embolic events in this current study.

Conclusions

Endocrine disorders are very common among multi-transfused β-TM patients which unfortunately are not detected on time in resource limited countries like India. Ferritin concentrations are not a reliable and sensitive predictor of these complications. In the current study, there was significant growth delay present in the patients suffering from Beta thalassemia. Growth delay not only causes a physical constraint on a children but also effects their psychological wellbeing. Early detection of growth and endocrine abnormalities not only will improve the overall health of the patients but will also reduce the economic burden of chronic illness on the family.

In this study, we observed that average weight for age group in 5-10 years was 18.3 kg with SD of 4%. The average weight of 11-18 years was 31.9 with SD of 8.9. In terms of height the average height of 5-10 years was 106.9 with SD 11.8 and height of 11-18 years was 139.3 with SD of 14.4. Both age group had low BMI of 16.61 kg/m^2 with SD 5.34 and 16.29 kg/m^2 with SD of 2.91 in 5-10 years and 11-18 years age group respectively.

Also, there was a significant growth delay in 82.6% (114) with $p<0.0001$. Therefore, proper endocrine evaluation and prompt management should be started in thalassemic patients at early age so as to prevent growth retardation and other related complications.

Limitations

1. It was a cross sectional observational study. A follow up study would have given a better picture.
2. Cardiac MRI and liver iron content could not be done due to unavailability of the same in the setup.

Due to lack of resources and ignorance, thalassemia may remain undiagnosed in 5-10 year old children.

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