Original Research Article

Prevalence of hypoparathyroidism, growth retardation in patients of β -thalassemia majorNaresh Manne¹, Sandeep Kumar Yadav¹, Bharat Kumar Gupta^{1,*}, Saurabh Singhal², Archana Dubey³¹Dept. of Biochemistry, Subharti Medical College, SVSU, Meerut, Uttar Pradesh, India²Dept. of Medicine, Subharti Medical College, SVSU, Meerut, Uttar Pradesh, India³Dept. of Paediatrics, Subharti Medical College, SVSU, Meerut, Uttar Pradesh, India

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ABSTRACT

Background: Beta-Thalassemia is a genetic disorder which is associated with a lot of complications. Frequent blood transfusions result in increased iron deposition in various tissues leading to dysfunction of many vital organs. Endocrine disorders constitute a major part of such complications increasing the morbidity of thalassemia manifold in the affected patients. Early diagnosis of hypoparathyroidism (HPT) could prevent other severe disorders such as Tetany, seizures, osteopenia, and osteoporosis. Growth retardation can occur as complication of thalassemia as early as the 1st or 2nd year of life but these abnormalities more prominent after the 6 – 8 years of life.

Aim & Objectives: The aim of this study was carried out to determine; 1. The prevalence of Hypoparathyroidism (HPT) and Growth retardation in patients with beta thalassemia and to correlate them with serum ferritin, calcium, phosphorus and alkaline phosphatase levels; 2. The relationships of growth failure with certain variable including age, serum ferritin, mean hemoglobin level and gender of the patients.

Materials and Methods: This is a descriptive cross sectional research study which was conducted on 200 subjects (100 cases and 100 controls) in the age group of 10-25 years who had visited the OPD/IPD of Subharti Medical College & affiliated Hospitals, Meerut. The cases included were with confirmed diagnosis of beta thalassemia major, with regular blood transfusions and serum ferritin levels >2000 ng/ml irrespective of chelation therapy.

Results: Out of 100 patients, Hypoparathyroidism was diagnosed in 18% patients, Growth retardation/Short stature 93% and Weight loss was found in 93% patients. The mean age at diagnosis was 12.6 years (range 11-16 years), mean serum calcium was 7.53 mg/dl (range 7.58-9.04 mg/dl), mean serum ferritin was 5831.0 ng/ml (range 2000-8,064 ng/dl) and mean serum phosphate was 5.63 mg/dl (range 4.50-7.73 mg/dl). Serum parathyroid hormone (PTH) levels were low in most of the patients. Short stature was observed in most of the patients, while it was found normal in control subjects.

Significant Hypoparathyroidism (HPT) observed along with growth retardation in beta thalassemia patients ($p < 0.001$). A significant decrease in serum calcium level was seen in cases when compared to controls, where as the levels of both serum phosphorus and alkaline phosphatase levels were found increased in cases as compared to control.

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1. Introduction

β -Thalassemia represents a group of recessively inherited hemoglobin disorders characterized by reduced synthesis

of β -globin chains leading to the synthesis of hemoglobin with an impaired oxygen binding capacity.¹ The advent of safe transfusions with adjuvant chelation therapy has dramatically improved the life expectancy of patients with β -thalassemia major (BTM), who can now survive into their fourth and fifth decades of life.² However,

* Corresponding author.

E-mail address: anchitbharat@hotmail.com (B. K. Gupta).

frequent blood transfusions have been associated with iron overload, which may result in endocrine abnormalities mainly hypogonadism, diabetes mellitus, Short stature, and hypoparathyroidism (HPT).³ HPT is one of the most important endocrine complications of BTM. The most important factors attributed to this complication are the deposition of iron in parathyroid gland leading to gland dysfunction and the possible suppression of parathyroid secretion induced by bone resorption resulting from increased hematopoiesis secondary to chronic anemia.⁴ HPT may be presented by neurological abnormalities that include latent tetany, seizures, laryngeal, stridor, osteopenia, osteoporosis and paresthesia in the hands or in the region of the lips.⁵ Osteoporosis represents an important cause of morbidity in the thalassemic population. Even well-transfused patients with normal gonadal function who are supplemented with calcium show low bone mass by dual-energy x-ray absorptiometry suggesting other factors are also involved.⁶

On other hand the Normal growth of β -thalassemia children during first 10 years of life depend upon the maintenance of Hb level above 8.5 gm/dl, during this period of child life hypoxia may be the main factor retarding growth and the maintenance of Hb levels above 10-11 gm/dl together with adequate iron chelation therapy makes the β -thalassemia patients indistinguishable from their non thalassemia peers.⁷ Growth retardation in thalassemia can occur as early as the 1st or 2nd year of life but these abnormalities are more prominent after the 6-8 years of life.⁸ After the age of 10 years despite the fact that adequate level of hemoglobin are maintained, many of the β -thalassemia children start having decelerate growth. In pubertal children, there may be a reduced growth spurt with marked deceleration, for which iron over load may be responsible.⁷

2. Materials and Methods

We conducted this research on 100 diagnosed Beta thalassemia major patients as study cases, who had visited the OPD/IPD of Subharti Medical College & CSSH and Lokpriya Hospital, Meerut for routine blood transfusion or for any other complication. Total 100 healthy age and sex matched individual who volunteered themselves for study were included as controls.

Due Ethical clearance from IEC was obtained in advance and written informed consent was taken from patients/guardians/controls prior to include them as study population. A Questionnaire was framed covering the key points of clinical history of illness and treatment with family background. Relevant clinical examination and investigations were carried out to establish the diagnosis of Hypoparathyroidism and Growth retardation.

2.1. Inclusion criteria

1. Age 10-25yrs.
2. Confirmed cases of β -thalassaemia major
3. Patients undergo regular blood transfusion..

2.2. Exclusion criteria

1. Patients with primary endocrinopathy.
2. Patients with any other chronic illness.
3. Other type of haemoglobinopathies.

2.3. Methods

1. An Iron overload was determined by a measurement of serum ferritin concentrations using Chemiluminescence Immunoassay kit method by Siemens Advia Centaur-XP fully automated analyzer;⁹ Normal reference range: Male:12-322 ng/ml; Female: 12-290 ng/ml).
2. Serum intact parathyroid hormone was estimated by chemiluminescent immunoassay method by SIEMENS Advia Centaur-XP fully automated analyzer.¹⁰ Normal local reference value was from 40 to 65 pg/l.
3. Serum Calcium was estimated by OCPC kit method by SIEMENS Dimension-RXL-max fully automated analyzer.¹¹ Normal local reference value was from 8.5 to 10.1 mg/dl.
4. Serum Phosphorus by Modified phosphomolybdate kit method by SIEMENS laboratories.¹² Normal local reference value was from 2.6-4.7 mg/dl.
5. Serum Alkaline phosphatase by enzymatic, p-Nitro Phenyl Phosphate, AMP buffer method. SIEMENS dimensions RXL-max.¹³ Normal local reference value was 45-116 U/l.
6. Growth parameters were measured for all patients and control group including height, weight.
7. Height was measured using an age appropriate stadiometer (all measurements were obtained in centimeter and plotted on the centile chart). Short stature is that height below 3rd centile for age and gender based on growth velocity chart.¹⁴
8. Weight was measured by weight scale (all measurement were obtained in kilogram and transformed into centile chart) and the case considered is positive if the weight is below 3rd centile for age and gender.¹⁴

Hypoparathyroidism was diagnosed if patients displayed all of the below criteria:

1. Intact parathyroid hormone (PTH) less than 10 pg/l.
2. Serum calcium less than 8.5 mg/dl.
3. Increased serum phosphate.
4. Normal or increased alkaline phosphatase levels.

Other parameters analyzed included age, sex, serum ferritin levels, age of onset of HPT, any symptoms of Hypocalcemia.

3. Results

This study comprised of 100 cases and 100 controls. Cases included 39 female and 61 male patients. The mean serum ferritin level among cases was found 5831.00ng/ml. Data Analysis is done using SPSS software version 18. Results are specified in tables and graphs as below.

Out of 100 thalassemia patients there were 18 patients had detected HPT which includes 6 females and 12 males their mean age is 12 years and 82 patients were not affected by this disorder. The mean serum levels of PTH, Calcium, Phosphorus and ALP in patients were 5.14pg/l, 7.53mg/dl, 5.63mg/dl 355.18 U/L respectively. The mean and SD of serum ferritin level was 5831.0 ± 2860 ng/dl.

There were a total of 93% patients detected to be having short stature. This included 57 males and 39 females with growth retardation and weight loss was identified 86%; their mean serum ferritin level was above 3998.57 ± 2573.90 ng/dl and the mean Hb level 8.22 ± 1.86 g%. As per growth velocity chart 93 patients were below 3rd centile based on age and gender marked as negative (-ve) cases and 7 patients were above 3rd centile marked as positive(+ve) cases.

Fig. 1: Status of hypoparathyroidism in case control subjects

Fig. 2: Status of Growth retardation in case, control subjects

4. Discussion

HPT is a well-known complication in patients with BTM, but it is thought to be uncommon, and its incidence is considered to be decreasing with improvements in chelation therapy. A number of possible mechanisms have been described to be responsible for glandular damage through iron overload.¹⁵ These include free radical formation and lipid peroxidation, resulting in mitochondrial, lysosomal, and sarcolemmal membrane damage; a number of surface transferrin receptors in the cell; and the ability of the cell to protect itself against inorganic iron, but the reason why some patients develop HPT and others do not is not exactly known.¹⁶

The objective of the current study was to assess the prevalence of HPT and Growth retardation in patients with β -thalassemia. A total of 100 patients were included in this study, and their mean age was 15 ± 5.63 years. The selected patients were older than 6 years to better detect the effect of iron overload complications and chelation effects.

In the present study, we reported the incidence of HPT was 18% in a total of 100 TM patients. Our results are similar to the other studies done by Bazi A et al.(2018) In addition, the incidence of HPT was estimated at 18.6-21.7% in previous studies which were done in other areas of the world.^{16,17}

The patients with HPT in our study were significantly older (15.1 ± 5.8) years than patients without HPT (9.2 ± 4.2) years. Furthermore, a significant difference was observed regarding the mean blood received per transfusion between TM patients with and without HPT. In consistence with these findings, HPT was associated with the age of TM patients in some reports,¹⁸ while other studies did not confirm this relationship;¹⁹ The majority of patients with HPT had irregular iron chelation regimens.

De Satictis et al.²⁰ observed 24 cases of BTM and HPT of variable severity. Their mean age when HPT was diagnosed was 16.5 years (11–24 years). Olivieri et al.²¹ found that 22% of their patients with thalassemia had endocrine complications, with a serum ferritin level above 2000 μ g/l.

In our study 27% the cases had low serum calcium levels and high serum phosphorus levels indicating damage to the parathyroid gland function. The maintenance of a normal serum calcium concentration depends on the balanced actions of PTH, vitamin D, and, to a lesser extent, calcitonin.²²

In line with our result, Basha et al.²³ studied 40 patients with BTM and 15 controls, and their age ranged from 2–18 years. They observed a significant decrease in PTH and serum calcium levels and a significant increase in both serum phosphorus and alkaline phosphatase levels in patients with β -thalassemia and this goes with our study.

In our study, there were nonsignificant differences between those who had HPT and those who did not

Table 1: Demographic, hematological and biochemical characteristics of cases and controls

S. No	Name of Parameter	Cases(n=100)	Controls (n=100)	P Value
1	Age (in year)	15±5.63	16±5.15	P >0.001
2	Height (centimeter)	118.07±22.82	123.13±19.04	P<0.001
3	Male Female ratio	61: 39	57:43	P<0.001
4	Weight (Kgs)	27.32±9.86	30.68±8.93	P <0.001
5	Haemoglobin (gm%)	8.22±1.86	12.9± 3.44	P <0.001
6	Serum ferritin (ng/ml)	5831.0±2860	46.48±83.1	P<0.001
7	Serum Parathormone (pg/L)	5.14±1.28	30.36±10.85	P <0.001
8	Serum Calcium (mg/dl)	7.53±2.11	9.58±1.48	P <0.001
9	Serum phosphorus(mg/dl)	5.63±1.16	3.57±0.78	P <0.001
10	Serum alkaline phosphatase(IU/L)	355.18±185.52	208.32±79.67	P <0.001

Table 2: Status of hypoparathyroidism in case control subjects

HTP status	Cases	Controls	P value
Hypoparathyroidism	18	0	p-value < 0.001, significant
Normal	82	100	
Total	100	100	

Table 3: Status of growth retardation in case control subjects

Status of Short stature	Cases	Controls	P value
Growth retardation	93	0	p-value < 0.001, significant
Normal	07	100	
Total	100	100	

Table 4: Growth parameters in thalassemic patients and control group

	Height		Weight		Total
	+ ve cases*	- ve cases*	+ve cases	- ve cases	
Thalassemic patients	93 93%	07 07%	86 86%	14 14 %	100
Control group	6 6 %	94 94%	8 8%	92 92%	100

*+ve cases mean below 3rd centile *-ve cases mean above 3rd centile

There was a highly significant difference of growth retardation (height and weight) among thalassemic patients, in comparison to control group. p-value < 0.001.

Table 5: Relation of growth parameters to age in thalassemic patients

Age	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<5 years	26 (89%)	03 (11%)	24 (82%)	05 (18%)	29
≥5-10	16 (73%)	06 (27%)	17 (78%)	05 (22%)	22
≥10-15	28 (84%)	05 (16%)	22 (66%)	11 (34%)	33
≥15 years	14 (88%)	02 (12%)	09 (57%)	7 (43%)	16
Total	84	16	72	28	100

There was a highly significant difference of growth retardation of both height and weight with increasing age of patients more than 10 years. P –value < 0.

Table 6: Relation of growth parameters in thalassemic patients to level of serum ferritin

S. Ferritin ng/dl	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<1000	06 (80%)	02 (20%)	08 (100%)	00 (0%)	08
≥1000-2000	13 (76%)	04 (24%)	09 (52%)	08 (48%)	17
≥2000	68 (91%)	7 (09%)	63 (84%)	12 (16%)	75
Total	87	13	44	66	100

There was a significant difference of short stature with increasing level of serum Ferritin (of more than 1000 microgram / liter). P <0.005.

Table 7: Relation of growth parameters in thalassemic patients to mean Hb- level

Mean Hb level	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<7	37 (59%)	25 (41%)	32 (51%)	30 (49%)	62
≥ 7-9	18 (85%)	03 (14%)	11 (52%)	10 (48%)	21
≥9	12 (71%)	05 (29%)	14 (82%)	03 (18%)	17
Total	67	33	57	43	100

There was a highly significant difference of growth retardation with decreasing mean hemoglobin level of (below 8 gm/dl). P- value < 0.001.

regarding transfusion and chelation therapy, serum ferritin, or hemoglobin level, which may suggest either an individual sensitivity to iron toxicity or early damage of the parathyroid gland before chelation had reduced the iron overload.

Growth retardation is frequent in patients with BTM and becomes more evident at puberty stage because of the lack of growth spurt.²⁴ This occurs because of many factors, including chronic anemia, folate deficiency, direct iron toxicity, and endocrine disorders.²⁵

In the current study, we found there was a high prevalence of Growth retardation (93.2%) and weight loss (86%), but there were nonsignificant differences between single and combination therapy groups regarding frequency of delayed puberty or the frequency of short stature. Our results are similar to other studies done in other areas of world.^{14,26} This indicate that thalassemic patient have a risk factors for growth failure as result from direct relation to iron toxicity especially endocrine gland, Intensive chelation therapy especially below 10 years of age²⁷ or may result from other factors like anemia, hypersplenism and Folate deficiency, Calcium and zinc deficiency.²⁸

Our result is higher than that the results done in other areas of world 62%,²⁹ 60%³⁰ and 57.7%.³¹ This could be explained by patients age included in this study, where most of our patients (62/100) above the age of 10 years while other studies were commonly done on patients below the age of 10 years. This study shows that growth failure associated with decreasing hemoglobin of below 9 gm/dl implicating chronic hypoxia as a cause.⁸

5. Conclusion

Based on the findings, The research concluded Growth retardation (86%) and HPT(18%) are common endocrinopathies in TM patients who were on regular blood transfusion therapy. Due to the possible reversal of these conditions at early stages using intensive iron chelation therapy, routine monitoring of patients who are at risk of these endocrinopathies is recommended. And the rate of growth failure is directly related to the age of patient, serum ferritin, hemoglobin level. As a preventive measure children with beta thalassemia major in their second decade of life need to be supplemented with calcium and vitamin D to prevent the Hypocalemia and hypocalcemic tetany, to facilitate

bone growth. This study emphasized the importance of maintenance of normalized hemoglobin level, measurement of parathyroid hormone on a regular basis, good monitoring of growth parameter and iron over load with optimal iron chelation therapy.

6. Source of Funding

None.

7. Conflict of Interest

None

8. Ethical Clearance

Granted by institutional ethical committee, SMC, SVSU Meerut.

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Author biography

Naresh Manne Assistant Professor

Sandeep Kumar Yadav Assistant Professor

Bharat Kumar Gupta Professor and Head

Saurabh Singhal Professor

Archana Dubey Professor

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