Prevalence of short stature in transfusion dependent beta thalassemia patients in a tertiary care centre in North East India

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ABSTRACT

Background: beta thalassemia is one of the most common hereditary hemoglobinopathy requiring regular blood transfusion to help reduce the complications of anemia and allow normal growth in children. Materials and Methods: It was a cross-sectional study done on 50 numbers of transfusion dependent beta thalassemia patients between 18 months and 18 years of age in North east India. Growth parameters like weight, height, BMI were recorded. Results: Overall prevalence of stunting was 68%, a significant association was found between stunting and religious connotation.

Keywords: Beta thalassemia, hemoglobinopathy, short stature, stunting, stunting in thalassemia, thalassemia

Introduction

Thalassemia is one of the major public health problems, as the carrier rate and disease incidence is increasing worldwide. It refers to a group of genetic disorders of globin chain production, in which there is an imbalance between the alpha globin and beta globin chain production. Also known as Cooley's anemia, it is characterized by pallor, hepatosplenomegaly, jaundice, growth retardation, and bone changes due to extramedullary hematopoiesis causing [Figure 1] shows a child with hemolytic facies.

Children are usually asymptomatic at birth and become symptomatic after the normal physiological phenomenon of “switch over” from fetal to adult hemoglobin takes place, that is, at around 4 to 6 months after birth. According to the severity, thalassemia is clinically divided into thalassemia major, thalassemia intermedia, and thalassemia minor or thalassemia trait.

Hb E is an extremely common structural $\beta$-hemoglobin variant that occurs frequently in many Asian countries. Hb E $\beta$ thalassemia is a thalassemia syndrome of intermediate variety with a varied clinical spectrum. On one end, patient presents like severe form of thalassemia major while at the other end, they might grow and develop normally without the need of blood transfusion.[1]

India has the largest number of children with thalassemia major in the world—about 1 to 1.5 lakhs and almost 42 million carriers of beta thalassemia trait. It is also important to remember that about 10,000 to 15,000 babies with thalassemia major are born every year.[2]

Thalassemia major as well as severe form of Hb E $\beta$ thalassemia constitute the major burden of disease management, as they require regular blood transfusions and iron chelation therapy. The thalassemia syndromes (thalassemia major or intermedia) are caused by inheritance of abnormal thalassemia genes from both carrier parents,
or abnormal thalassemia gene from one parent and an abnormal variant hemoglobin gene (Hb E and Hb S) from the other parent.[6]

While bone marrow transplantation is the only definite treatment, blood transfusion therapy dramatically improves the quality of life and reduces complications of severe thalassemia. However, transfusion-induced hemosiderosis becomes the major clinical complication of transfusion-dependent thalassemia.

Iron overload in the transfusion dependent thalassemia patients is the result of multiple blood transfusions, ineffective erythropoiesis, increased gastrointestinal absorption of iron, and lack of physiologic mechanism for excretion of iron.[9] Introduction of regular transfusion and chelation therapy has increased lifespan and improved quality of life. Despite this approach, a significant proportion of the children continue to have problems with growth and puberty. The cause of short stature is multifactorial but is mainly due to iron overload.[14]

**Aims**

1. To study the prevalence of short stature and abnormal glucose tolerance among transfusion-dependent thalassemia patients.
2. To find out relationship between serum ferritin levels and short stature in transfusion-dependent thalassemia patients.

**Materials and Method**

The study was undertaken in the Department of Pediatrics, in a tertiary care center in northeast India. Data were collected from all the thalassemia patients (only confirmed by Hb electrophoresis) between 18 months to 18 years with inclusion and exclusion criteria highlighted below. Growth parameters like weight, height, and body mass index were recorded. Figure 2 and Figure 3 show instruments used in this study. Ethical clearance was obtained from the institute’s Ethical clearance committee. Consent for participation in the study was taken from legal guardian.

Short stature was considered as height below 3rd centile or more than –2 SD below the median height for age and gender according to the population standard. WHO growth charts were used for interpretation of the data. In cases above 2 years of age, standing height was taken using a stadiometer. In children below 2 years, supine length was measured using an infantometer with a rigid headboard on one side and a moveable footboard on the other side while holding the infant straight on the horizontal board.

**Results and Observations**

In our study, we included a total of 50 children with transfusion-dependent thalassemia namely, thalassemia major and Hb E β thalassemia. All the children attended the study center for blood transfusions. Figure 4 shows a thalassemia patient receiving blood transfusion at the centre. It was a cross sectional study done within the time frame from June 2019 to May 2020. All included were diagnosed cases by hemoglobin electrophoresis or High-Performance Liquid Chromatography and were already started on blood transfusion therapy for their anemia.

Contingency tables were made to determine the prevalence of short stature and also relationship of short stature multiple independent risk factors like age, sex, serum ferritin levels, and ethnicity. Pearson's chi square test was carried out to determine if there is any significant association between stunting and any other risk factors. All calculations were done using 95% confidence interval and P value less than 0.05 was taken as significant. All calculations were done using MS Excel and SPSS (24.0).

**Discussion**

We found overall stunting in our study as 68% [Table 1]. It was similar to Hashemi et al.[7] who found height less than five centile in 65.71%, Hamidah et al.[8] found prevalence of short stature in 54.5%, Moayeri et al.[9] showed that 62% were less than –2 SD, Fadlyana et al.[10] got 62% of short stature, and Jana et al.[11] got 65.8%.

It was contradictory to the findings of Kattamis et al.[12] who found it to be 35.3% among the Greeks and 37% among the Italians, Isik et al.[13] found 25.5% of stunting in their study, Roth et al.[14] found 40.6% of patients were short in stature (height below third centile). Soliman et al.[15] reported 49% of short stature (≤-2 SD), Borgna-Pignatti et al.[16] 40.6%, and Vogiatzi et al.[17] got 25%.

The higher prevalence could be due to the underlying malnutrition or irregular frequency of blood transfusions or compliance to chelation therapy.

| Table 1: Prevalence of stunting |
|---------------------------------|
| Height for age | Numbers | Percentage |
| Normal | 16 | 32% |
| Stunted (≤ -2 SD) | 34 | 68% |

| Table 2: Sex distribution of stunting |
|-------------------------------------|
| Z score (Height for age) | Males | Females | Total |
| >-1 | 4 | 3 | 7 (14%) |
| ≤-1 to -1.9 | 6 | 3 | 9 (18%) |
| ≤-2 to -2.9 | 7 | 8 | 15 (30%) |
| ≤-3 | 14 | 5 | 19 (38%) |
| Total | 31 (62%) | 19 (38%) | 50 (100%) |

| Table 3: Distribution of cases based on religion |
|---------------------------------|
| Religion | Number | Percentage |
| Hindu | 28 | 56% |
| Islam | 22 | 44% |
We found that stunting was almost equal in males and females, although the total number of female subjects in our study was less. It was 67.7% in males and 68.4% in females [Table 2]. There was no significant association found between gender and stunting which was similar to Hamidah et al., male 50% versus female patients 60%, Najafipour et al. found 70% of males and 73% of females had stunting, Kwan et al. found 75% of males and 62% of females to be of short stature, and Tienboon et al. also did not find any gender difference in stunting.

It is difficult to interpret cross sectional studies on growth of thalassemia patients with different transfusion regimens. Due to late presentation only on being symptomatic mostly, irregular frequency of blood transfusions, and variable compliance to chelation therapy in our study subjects which would undoubtedly affect their growth, apart from iron overload itself.

Out of the 68% found to be stunted in our study, 46% were found to be both stunted and wasted and 22% were only stunted. This indicates the prevalence of chronic malnutrition among the study subjects.

There is a significant association (P = 0.014) between stunting and religious connotation, with stunting being more prevalent among the Muslims, 86.4% [Table 3]. This can be explained by the fact that most Muslim patients were from rural areas and border districts which have low socioeconomic condition and thus at high risk for underlying malnutrition [Chart 1].

No significant association was present between serum ferritin level and stunting among the study participants (P > 0.05). Similarly, Gomber et al. found no relation between physical growth and serum ferritin levels. Also, Isik et al. did not find any correlation between mean ferritin levels and height for age.

Contradictorily, Pemde et al. found positive correlation between age and mean ferritin level (correlation coefficient [r] = 0.6085, P = 0.0000), Shalitin et al. found high serum ferritin levels related to short stature, Fadlyana et al. got significant correlation between serum ferritin levels and stunting, and Hashemi et al. found mean serum ferritin significantly higher in patients with a final short stature (P = 0.05).

This could be because of the fact that the cause of growth failure in thalassemia cases is multifactorial like chronic hypoxic insult to the growing bone cells, ineffective erythropoiesis, underlying malnutrition, irregular treatment, etc., apart from the toxicity of iron overload.

A systematic review and meta analysis using 74 studies, of stature complications in Beta thalassemia major patients in 2021, showed that nearly half of the patients suffer from growth impairment. The chronicity and in particular the lifelong treatment aspect of this disease imposes a heavy psychosocial burden to these patients and their families. Its chronic treatment is a permanent reminder to get depressed and causes difficulty in leading a normal life.

With early prenatal screening and detection, it is possible to diagnose a congenital defect. Lack of awareness among primary health care providers regarding possibility of screening can lead to an increase in the incidence of disease.

Thus, this study emphasizes the need for primary care physicians to help in awareness of the families regarding the possibilities and need of prenatal screening with regard to hereditary disorders specially in societies with consanguinity as norm. And also their role in monitoring the growth in affected children for early intervention and referral as and when needed.

**Summary**

A total of 50 patients were included in this study. Overall, prevalence of short stature was 68%. The prevalence was significantly higher in children from rural background (P < 0.05). Short stature was almost equally present in males and females with no significant association between gender and stunting. A significant association between stunting and Muslim children from rural background was found in this study.

**Conclusion**

Our study is reflective of the high prevalence of stunting in transfusion-dependent thalassemia patients, especially among those from rural areas with poor socioeconomic conditions, with an underlying chronic nutritional deficit. A regular follow to maintain optimum pretransfusion hemoglobin level is important to prevent the complications of this disease, mainly growth abnormalities specially in the younger age group, as chronic anemia and ineffective erythropoiesis are known to be detrimental to growth. Hence, this study highlights the need of monitoring growth parameters, at least 6 monthly, in the transfusion-dependent thalassemia patients by primary physicians so as to prevent complications causing morbidities.

![Chart 1: Region wise distribution of cases](image-url)
Low socioeconomic background and lack of awareness among patients and families can be risk factors for growth faltering in transfusion-dependent thalassemia patients.

There is a need for creating awareness regarding the nature of the problem and vitality of regular follow-up in these patients.

Government supported prevention and screening programs need to be implemented for these genetic defects for better overall outcome to the nation as such, as evident from exemplary screening programs of Cyprus, Greece, Iran, and Pakistan, which now have a reduced incidence of the disease. It would be a huge relief to the public health burden.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References
1. Fucharoen S, Weatherall DJ. The hemoglobin E thalassemias. Cold Spring HarbPerspectMed 2012;2:a011734.
2. National Health Mission Guidelines on Hemoglobinopathies in India (2016) Prevention and Control of Hemoglobinopathies in India. National Health Mission, Ministry of Health & Family Welfare, Government of India.Available from: http://nhm.gov.in/images/pdf/programmes/RBSK/Resource_Documents/Guidelines_on_Hemoglobinopathies_In%20India.pdf.
3. Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Pica A, Meleverdi C, et al. Survival and causes of death in thalassemia major. Lancet 1989;2:27-30.
4. Gabutti V, Piga A. Results of long-term iron-chelating therapy. Acta Haematol 1996;95(2):26-36. doi:10.1159/000203853. PMID:8604584.
5. Verma IC, Choudhry VP, Jain PK. Prevention of thalassemia: A necessity in India. Indian J Pediatr 1992;59:649-54.
6. Harsha Y. Post counseling follow-up of Thalassemia in highrisk communities. Indian Paediatr 1997;34:1115-8.
7. Hashemi A, Ghillian R, Golestan M, Akhavan GM, Zare Z, Dehghani MA. The study of growth in thalassemic patients and its correlation with serum ferritin level. Iran J Pediatr Hematol Oncol 2011;1:147-51.
8. Hamidah A, Rahmah R, Azmi T, Aziz J, Jamal R. Short stature and truncal shortening in transfusion dependent thalassemia patients: Results from a thalassemia center in Malaysia. Southeast Asian J Trop Med Public Health 2001;32:625-30.
9. Moayeri H, Oloomi Z. Prevalence of growth and puberty failure with respect to growth hormone and gonadotropins secretion in beta-thalassemia major. Arch Iran Med 2006;9:329-34.
10. Fadlyana E, Ma'ani F, Elizabeth M, Reniarti L. Correlation between serum ferritin level and growth disorders in children with thalassemia. Am J Clin Med Res 2017;5:31-5.
11. Kattamis C, Liakopoulou T, Kattamis A. Growth and development in children with thalassemia major. Acta Paediatr Scand 1990;366(Suppl):111-7.
12. Isik P, Yarali N, Tavil B, Demirel F, Karacam GB, Sac RU, et al. Endocrinopathies in Turkish children with Beta thalassemia major: Results from a single center study. PediatrHematol Oncol 2014;31:607-15.
13. Roth C, Pekrun A, Bartz M, Jarry H, Eber S, Lakomek M, et al. Short stature and failure of pubertal development in thalassaemia major: Evidence for hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion. Eur J Pediatr 1997;156:777-83.
14. Soliman AT, Elzalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion-dependent children and adolescents with thalassaemia major and sickle cell disease: A comparative study. J Trop Pediatr 1999;45:23-30.
15. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A systematic review and meta-analysis of stature growth complications in β-thalassemia major patients. Ann Global Health 2021;87:48.
16. Kurian MA, Li Y, Zhen J, Meyer E, Hai N, Christen HJ, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: An observational cohort and experimental study. Lancet Neurol 2011;10:54-62.