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Skeletal Radiological Findings in Patients with Beta Thalassemia Major Visiting a Tertiary Care Facility

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Abstract

Objective: To determine the frequency of common skeletal radiological findings in patients with Beta Thalassemia major (βTM) visiting tertiary care facility, Hyderabad.
Methodology: This descriptive cross-sectional study was conducted at paediatric ddepartment of Pediatrics, LUMHS/Jamshoro from August 15, 2022 to February 16, 2022. Children with beta thalassemia major aged 2 to12 years of either gender presented with bone pain on physical activities were included. Radiological skeletal findings such as trabeculation, rib widening, and facial bone deformity were observed. Relevant data of study was entered and analyzed by using SPSS version 26.
Results: Of 170 participants, facial bone deformity was observed in 30.6%, trabeculation in 9.4%, and ribs widening in 21.8% patients. A significant association of facial bone deformity was observed with female gender (p=0.006) and prolonged duration of disease (p=0.002). While trabeculation was found insignificantly associated with age, gender and duration of disease (p = >0.05). However, the frequency of ribs widening was significantly associated with gender (p=0.038), while its was insignificantly associated with duration of disease and age of the children (p = >0.05).
Conclusion: This study revealed important insights into the skeletal radiological framework of patients with Beta Thalassemia major in terms of facial bone deformity, trabeculation, and ribs widening underscores the substantial burden of skeletal manifestations in this population.
Keywords: Beta Thalassemia major, bone deformity, trabeculation, ribs widening

Introduction

The Beta-thalassemia major, also identified as Cooley's anemia or transfusion-dependent thalassemia, is one of the most prevalent inherited hemoglobinopathies throughout the world. It is resulting from mutations in the β-globin gene located on chromosome 11, leading to severely deficient or lack of β-globin chains synthesis, subsequent imbalance of α/non-α globin chains, unproductive erythropoiesis, and the severe hemolytic anemia among patients.[1] The worldwide burden of βTM is significant: around 60,000 infants are born with βTM per year, for the most part in developing nations, with approximately 1.5% of the population of world, expected at 80 to 90 million individuals carrying related mutations.[2] According to a systematic review of 2023 by Musallam et al, demonstrated that the highest burden remains concentrated in the Middle East, South Asia, and Mediterranean regions, though migration has led to rising prevalence in the Northern Europe and the North America.[3] According to another recent comprehensive analysis of the Global Burden of Disease Study further underscored significant disparities in the prevalence, incidence, and disability-adjusted life years (DALYs) of thalassemia across many countries, highlighting its constant relevance as a major public health concern.[4] However in Pakistan, thalassemia affects around 5–7% of the population, placing the country among those with the largest number of patients dependent on regular transfusions of blood.[5]

Furthermore, the underlying pathophysiology of βTM triggers a cascade of systemic complications, as well as the skeletal alterations are among the earliest and most clinically significant presentations. Due to the absence of or with inadequate therapy of transfusions, the body attempts to compensate for chronic anemia through intense medullary and extramedullary hematopoiesis. Such compensatory marrow development results in a wide spectrum of radiological skeletal changes affecting both the axial and appendicular skeleton.[6] Among these the axial skeleton is predominantly affected in the skull, facial bones, paranasal sinuses, and vertebral bodies,

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while the appendicular skeleton shows more pronounced alteration in the long bones, ribs, hands and feet.[7] The particular radiological findings including facial bone deformity, coarse trabeculation, and rib widening represent well-recognized skeletal consequences of marrow hyperplasia and have been documented in both transfusion-dependent and non-transfusion-dependent populations of children with βTM.

Though, with the institution of regular hyper-transfusion programs and iron chelation therapy, the frequency and the severity of these classic radiological findings have gradually reduced over recent years. Regardless of this, skeletal manifestations have not disappeared completely, as marrow remains hyperactive in several cases of patients βT, and new skeletal complications attributable to therapeutic agents including deferoxamine-induced dysplasia and bisphosphonate- associated alterations have appeared.[7] According to a recent study by Sadri et al reported that the thalassemia patients show a significantly higher prevalence of osteoporosis and joint complications compared to controls, with DEXA scanning of the femur and lumbar spine revealing widespread reductions in bone mineral density.[8] Correspondingly, a hospital-based observational study proved clinically and radiologically significant skeletal compromise, observing that inadequately transfused patients remain at substantially higher risk for bone deformity and fracture of bones.[9]

Beyond the low bone mineral density, the craniofacial deformities remain a frequent and worrying complication. As according to a recent study conducted in 2025 reported the craniofacial deformity in 83% of βTM patients, with significantly raised serum ferritin and severe anemia (average Hb 6.57 g/dL) show a relationship with the severity of radiological bone fluctuations.[10] However the multifactorial pathogenesis of skeletal disease in βTM incorporating marrow hyperplasia, overload of iron, endocrine disorders, toxicity of the chelation therapy, inadequate nutritional status, and decreased physical activity makes a comprehensive radiological estimation essential for guiding clinical management of patients.[6,11]

Despite growing evidence, there remains a relative paucity of data from resource-limited settings, where access to adequate transfusion and chelation is inconsistent and classical skeletal manifestations may still be frequently encountered. As Pakistan has one of the highest beta-thalassemia carrier rates globally, while the generated radiological data at local level on skeletal complications remains unusual. Mostly published evidence originates from Mediterranean and South Asian cohorts with diverse transfusion adequacy, nutritional status, protocols of the chelation therapy, and socioeconomic profiles are differing substantially from the Pakistani population of beta thalassemia. Due to the, irregular transfusion, delayed diagnosis, and limited chelation access at local level may result in more pronounced skeletal manifestations. Hence present was conducted to determine the local data for prevalence and contribute evidence toward improving thalassemia management protocols in our population.

Methodology

This cross-sectional study was conducted over a period of six months, from August 2022 to February 2023, in the Department of Pediatrics at Liaquat University of Medical and Health Sciences, Jamshoro. A non-probability consecutive sampling technique was employed to recruit study participants. Ethical approval was obtained from approval of synopsis Ref no. CPSP/REU/PED-2020-164-5744. The sample size of 170 patients with beta thalassemia major was calculated using the WHO sample size calculator, keeping a confidence level of 95%, magnitude of trabeculation at 2.6%, and absolute precision at 2.4%. All the children aged 2–12 years of either gender, diagnosed with beta thalassemia major and presenting with bone pain during physical activities, were included. Children with chronic concomitant diseases such as chronic renal failure, chronic liver disease, primary endocrinopathies, osteomyelitis, septic arthritis, or those using medications affecting bone mineral metabolism were excluded. Informed consent was taken from parents after explanation for study objective and purpose. Complete medical history was obtained from parents including duration of disease, clinical examination was done and investigations were advised by the principal investigator like Hemoglobin level, serum ferritin, serum calcium and serum vitamin D level. A patient was labeled as having Osteopenia in case of a T score of -1 to -2.5. Radiological assessments were done by a qualified person having minimum 5 years' experience or more. The trabeculation was defined as the presence on plain radiographs of prominent, coarse, or dense trabecular striations traversing the medullary cavity, producing a

striated or lattice-like internal pattern of bone. The Rib widening was defined based on chest radiographs as the presence any one of the following features like a finger-like or flared appearance of the rib ends, or the presence of a radiolucent halo surrounding the anterior or posterior end of the rib. Additionally, the facial bone deformity was clinically evaluated and was considered present based on any one or more features from: frontal bossing involving the frontal and/or parietal bones, protruding or prominent zygomatic bones, saddle nose deformity, mongoloid slant of the eyes, or bulging cheekbones. All the information was collected by the study proforma. The data was entered and analyzed through statistical package for social sciences (SPSS) version 22.

Results

Overall mean age of 170 patients was 7.08 ±1.96 years and out of them 94 (55.3%) were males and 76 (44.7%) were females. The mean duration of disease was 4.14 ±1.83 years, mean serum hemoglobin level was 8.39 ±2.72 and mean serum ferritin level was 417.84 ±261.43 ng/ml. According to the common skeletal radiological findings, the facial bone deformity was observed in 52 (30.6%), trabeculation was in 16 (9.4%), and ribs widening were found in 37 (21.8%) patients as presented in table I.

Table I: Frequency of common skeletal radiological findings in patients with Beta Thalassemia major. (n=170)

Variables		N (%)
Facial bone deformity	Yes	52(30.6%)
	No	118(69.4%)
Trabeculation	Yes	16(9.4%)
	No	54(90.6%)
Ribs widening	Yes	37(21.8%)
	No	133(78.2%)

There was insignificant association was observed of bone deformity with age, as the deformity found in 32.5% of those aged >7 years and 29.0% of those patients aged ≤7 years (p = 0.628). On the other hand, it was significantly higher among females compared to males (39.4% vs. 19.7%; p = 0.006). The disease duration >4 years was also significantly related with deformity, compared ≤4 years (41.6% vs. 18.5%) (p = 0.002). Table II

Additionally, the trabeculation was insignificantly associated with age, gender and disease duration (>0.05) as shown in table III.

Moreover, the frequency of ribs widening was insignificantly associated with age of the children (p = 0.511), while its was significantly associated with gender as higher in females 27.7% compared to males 14.5% (p = 0.038). Likewise, the ribs widening frequency was also significantly higher among patients with disease duration >4 years (27.0%) in contrast to ≤4 years (16.0%) (p = 0.085), as shown in table IV.

Table II: Facial bone deformity according to age, gender and disease duration (n=170)

Variable		Facial Bone Deformity		Total	p-value
		Yes	No		
Age groups	≤7	27 (29.0)	66 (71.0)	93 (100)	0.628
	>7	25 (32.5)	52 (67.5)	77 (100)	
Gender	Male	15 (19.7)	61 (80.3)	76 (100)	0.006
	Female	37 (39.4)	57 (60.6)	94 (100)	
Duration of disease	≤4	15 (18.5)	66 (81.5)	81 (100)	0.002
	>4	37 (41.6)	52 (58.4)	89 (100)	

Table III: Trabeculation according to age, gender and disease duration. (n=170)

Variable		Trabeculation		Total	p-value
		Yes	No		
Age groups	≤7	8 (8.6)	85 (91.4)	93 (100)	0.691
	>7	8 (10.4)	69 (89.6)	77 (100)	
Gender	Male	7 (9.2)	69 (90.8)	76 (100)	0.936
	Female	9 (9.6)	85 (90.4)	94 (100)	
Duration of disease	≤4	5 (6.2)	76 (93.8)	81 (100)	0.168
	>4	11 (12.4)	78 (87.6)	89 (100)	

Table IV: Ribs widening according to age, gender and disease duration. (n=170)

Variable		Ribs Widening		Total	p-value
		Yes	No		
Age groups	≤7	22 (23.7)	71 (76.3)	93 (100)	0.511
	>7	15 (19.5)	62 (80.5)	77 (100)	
Gender	Male	11 (14.5)	65 (85.5)	76 (100)	0.038
	Female	26 (27.7)	68 (72.3)	94 (100)	
Duration of disease	≤4	13 (16.0)	68 (84.0)	81 (100)	0.085
	>4	24 (27.0)	65 (73.0)	89 (100)	

Discussion

The thalassemia represents a significant global health concern, posing a threat in most of the countries throughout the world,[12] and also associated with multiple skeletal complications resulting from persistent anemia and excess iron accumulation. This cross-sectional study estimated the radiological skeletal findings among 170 patients with beta-thalassemia major, with an overall mean age of 7.08 ± 1.96 years, which is consistent with the predominantly pediatric presentation of βTM, as the disease usually manifests between 6 to 24 months of age and is followed up throughout childhood. Consistently an Indian cohort by Santra et al[13] similarly demonstrated that a pediatric predominance with a mean age of 7.15 ± 0.9 years, closely reflecting to findings of this study. According to a comparative study from Mashhad, Iran, described an average age of the 100 βTM patient around 10.8 ± 4.4 years, which is slightly higher, likely reflecting a broader age range of enrollment.[14] Additionally a Pakistani study by Ashfaq et al[15] from the National Institute of Child Health Karachi enrolled children aged 5 to 15 years with an average comparable age group. Moreover, this study found a male predominance of 55.3% versus 44.7% females and this is aligning with multiple previous published studies, as a clinical profile study of thalassemia patients reported 74% males and females were 26%.[16] Likewise an Iranian study by Karimi et al[14] also reported a comparable male-to-female ratio, consistent with the observation that male cases are more frequently presented.[14]

In this study the mean serum hemoglobin level was 8.39 ± 2.72 g/dL, indicating moderate chronic anemia consistent with irregular or inadequate transfusion and mean serum ferritin level was 417.84 ± 261.43 ng/mL. In aligns to our findings a recent clinical profile study noted an average hemoglobin level of 9.7 ± 1.47 g/dL, which is slightly higher compared to this study and likely reflects better transfusion frequency in that population and they found also a higher mean ferritin level 2725.6 ± 2160.68.[16] Likewise a study of 86 βTM patients, stated a comparable mean hemoglobin level as 9.4 ± 0.7 g/dL among patients' group of beta thalassemia major.[17] Conversely, Mundu S et al[10] reported a lower mean hemoglobin of 6.57 ± 1.53 g/dL and raised mean serum ferritin level 4120.31 ± 2036.34 ng/mL in their Indian cohort, suggesting a more severe disease profile with poorer transfusion compliance. However, the study Sharif Y et al[18] reported the mean hemoglobin level as 8.01± 1.027 g/dL and mean ferritin level as serum ferritin 2773.3±1071.9ng/ mL. Comparatively the lower level ferritin in this cohort may indicate earlier presentation, younger age at admission or less duration of disease.

In this study the facial bone deformity was the most prevalent skeletal finding, observed in 52 patients (30.6%), followed by Trabeculation was identified in 16 patients (9.4%) and Rib widening was noted in 37 (21.8%) of the patients. Mundu S et al[10] reported craniofacial deformity in as many as 83% of their βTM cohort, with radiographic findings including thickened frontal bone in 93.3% and widened diploic space in 81.3% of the cases. In the study by Azizi V et al[19] reported that the bone abnormalities were observed in 47.94% of TI patients and 44.88% of TM patients, compared to 32.64% in the control group, with a statistically significant difference. On the other hand, according to Adamopoulos SG et al[6] the osteoporosis is considered one of the most clinically significant skeletal complications linked to β-thalassemia major disease. In aligns to our findings, Di Noto M et al[20] reported declined bone mineral density (BMD) in around 96.3% cases of beta thalassemia major with also substantially lowered trabecular bone score values.

Moreover, present study found facial bone deformity and Rib widening to be significantly associated with disease duration greater than four years ($p<0.05$), supporting the progressive, time dependent nature of this complication. These findings were supported by the Bedair EM et al[21] who stated that the intensity of skeletal changes varies according to the type of thalassemia, the severity and duration of the disease, the treatment regimen and frequency of blood transfusions, the adverse effects of transfusion and chelation therapy, and the particular affected bone. In the comparison to our findings, Wong P et al[22] demonstrated that the male patients with β-thalassemia showed more pronounced reductions in BMD and a higher rate of fractures compared to the females. However, the supporting to higher hemoglobin targets through regular transfusion particularly among male patients may help slow the decrease in BMD. The overall, the spectrum of skeletal radiological findings in this cohort confirms the ongoing burden of marrow hyperplasia-driven bone complications in Pakistani children with βTM, despite the availability of transfusion facilities. However,

this study poses several limitations, including limited sample sizes, not done the comprehensive biochemical analyses such as thyroid function, vitamin D, parathyroid hormone, and calcium levels, and lack of detailed bone deformity evaluation. The control group was also not incorporated, and the number of transfusions per patient was not systematically analyzed for skeletal problems. Therefore, further large-scale studies with comprehensive biochemical profiling and standardized skeletal evaluation are recommended to validate these findings and guide more effective treatment approaches.

Conclusion

In conclusion, study provides fundamental insights into the skeletal radiological landscape of patients with Beta Thalassemia major seeking care at a tertiary facility. The prevalence of facial bone deformity, trabeculation, and ribs widening underscores the substantial burden of skeletal manifestations in this population. Such findings underscore the need for comprehensive skeletal assessment and management strategies for patients with Beta Thalassemia major, particularly with regard to facial bone deformities which appear to be particularly prominent.

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