ORIGINAL ARTICLE
A COMPARISON OF SKELETAL AGE OF THALASSAEMIC PATIENTS OF 9–15 YEARS WITH CHRONOLOGICAL AGE BY RADIOGRAPHY

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Background: Thalassemia is inherited disorder characterized by haemolytic anaemia, due to complete absence or reduced β-globin chain synthesis, stimulating pathological bone marrow overstimulation and altered erythropoiesis. The change in bone mass ultimately results into miss interpretation of bone age once assed from x-ray radiograph. The aims compare skeletal age of thalassaemic children of 9–15 years with chronological age by x-ray wrist bones. **Methods:** This was cross sectional analytical study; the study was conducted in conjunction with Fatimid Hospital Peshawar Pakistan and Out Patients Department (OPD) of paediatrics for minor illness (other than Thalassemia) Khyber Teaching Hospital August 2014 to January 2015. A total 156 samples were selected convenient sampling to make comparison of bone age and chronological age between thalassaemic children (age 9–15years) and age sex matched normal control. A structure data collection check list was used to collect data X-ray findings (bone age). SPSS 20 was used for statistical analysis. **Results:** The results showed a total of 156 children with their mean age 11.9±2.2, male were 97 (62.2%) and females 59 (37.8%). Out of thalassaemic (n=76) majority 49 (62.8%) were male as compared to female 29 (37.2%). The mean chorological age among both of group were not significantly different (*p*=0.67). However, the bone age was significantly different from each other (*p*=0001). Pearson's correlation analysis revealed that was strong correlation between erupt teeth and bone age (r=0.462, *p*=0.0001). **Conclusions:** Skeletal age assessment was found to be suboptimal along with chronological age in children and adolescents suffering from thalassemia.
Keywords: Chronological age; B-Thalassemia Major; Bone age; Paediatrics; Sex matched

INTRODUCTION

Thalassaemia is a genetic disorder of the blood characterized by increased destruction of red blood cells, leading to haemolytic anaemia. The defective synthesis of either alpha or beta globin stimulates important pathologic consequences including, bone marrow overstimulation and altered erythropoiesis.[1]

It is a disease of childhood which is evident in the early few months of life, manifest as enlargement of heart and liver and a variety of bone disorders including osteopenia, bone pain, bone age delay, growth failure.[2] Growth of thalassaemic patient is relatively normal before 9–10 years of age after which absence or reduction in growth velocity and failure of pubertal growth spurts are observed. Height of thalassaemic patients is 2 SD below or less than 3 percentiles than mean age 13 as there are multiple pathologies of growth failure which cause impairment in height and sexual characteristics, along growth retardation dental problems are also common in them.[3,4] Age of an individual can be determined by various methods like skeletal age, chronological age, biological age, morphological age and dental age.[5] Skeletal age is determined by stages of ossification and a characteristic pattern of ossification of epiphyseal centres. Fishemn Ls proposed the use of ossification centres seen in hand wrist radiography and cervical vertebrae.[6] The developmental and structural changes in the lower end of ulna & radius, carpal bones, Meta carpal bones and phalanges have been used to study the skeletal maturity because they follow the pubertal growth spurt.[7]

Chronological age is the most apparent and determined developmental age, using child's date of birth, but varies from individual to individual.[8] Judgment of chronological age could be done by matching process, which comprise of comparison of a radiograph image of a subject to a defined reference that involves a sample of known sex and age. This comparative matching of bone, age and chronological age determination is mainly a measure of the biological maturity of bone that is converted to the chronological age by comparison with a reference.[9]

Children without any documentation of their date of birth only have less chance to provide medical care. When a child is incorrectly classified as an adult, the child is put at risk of a cycle that is disproportionate to the child's situation, age, or maturity.[10] Hence, a realistic definition of age is crucial to decide and treat children and juveniles appropriately and unregistered migrant children are at risk of abuse and

discrimination.[11] These differences in bone age and physical maturation necessitate the assessment of bone and chronological age among the children of local context suffering from Thalassemia. Aim of my study is to develop a reliable, feasible and cost-effective method to document growth retardation in thalassaemic children through skeletal age, for which I have performed various investigations like X-ray wrist bones and teeth counting, as growth retardation cause pubertal failure which is evident in adolescents. Children were chosen between 9–15 years of age, their bone age is then compared with chronological age. The best tool for age determination can be established in the treatment of patients with Thalassemia by comparing skeletal age of thalassaemic children of 9–15 years with normal values of control group. In this way their quality of life and social adjustment may be improved.

MATERIAL AND METHODS

This was cross sectional analytical study conducted in conjunction with Fatimid Hospital Peshawar Pakistan (a major Thalassemia care centre) and Khyber teaching Hospital Peshawar (Department of paediatrics). The study participants comprised of thalassaemic patients (children) aged 9-15 years including both males and females. The children with similar age, sex and height were selected from Out Patients Department (OPD) of paediatrics for minor illness (other than Thalassemia) Khyber Teaching Hospital. The Inclusion criteria were; (1) diagnosed cases of beta Thalassemia major patients 9–15 years of age, (2) not suffering from any serious hepatic, renal, cardiac diseases, diabetes mellitus or any other serious infections, (3) thalassaemic patients with known birth record. The exclusion Criteria included (1) children without precise birth records. (2) Thalassaemic patients with other metabolic or skeletal deformities not related to Thalassemia. (3) Radiographs not of sufficient quality or had poor positioning so that bone-age could not be determined. The list of thalassaemic patients was obtained from the centres (admission counter), The research team consists of a principal investigator and two research assistants. The data collection was carried out over a period of six months from August 2014 to January 2015. A written informed consent was taken from the study participants after conveying the purpose of the survey and ensuring confidentiality. A structure data collection check list was used in current study to manage the data. Hand wrist radiographs were performed on 76 of thalassaemic patients and normal control group of age 9–15 years. The radiographs allowed an assessment of the degree of maturation and the fusion of the epiphysis with the diaphysis of the radius bone. The technique consisted of an occlusal film positioned under the wrist, with the palm facing down. With an exposure time of 0.8 seconds, a 40 cm cone was positioned perpendicular to the position of the hand

and the film, and the radiographs were acquired. The films were processed on automated machine. After complete drying and identification these films were stored for evaluation. Hand radiographs from control and thalassaemic groups were obtained in the Khyber teaching Hospitals Peshawar using Philips Medical Systems Super 80 CP X-ray equipment (Philips, Eindhoven). X-ray exposure was 55–60 kV, 5 mAs, film focus distance 1m, and fine focal spot 0.6 mm.

Bone age was collected for each of the patients based on Greulich and Pyle's 1959 standards (GP2). All of the patient's bone age was assessed according to the GP2 atlas method. The findings were also reviewed by another certified radiologist to enhance the accuracy. The difference between the chronological and bone age was estimated. Data was analysed using SPSS 20.0. The frequency, proportion, percentages, ratio, means and SD were calculated. For continuous variables like age of respondents, means, mean difference and SD were calculated. For each of categorical variables like gender, ossification centres appearance frequency, proportion, percentages were calculated. The chi square test was applied to compare the ossification centres in wrist bones of thalassaemic patients with normal children. The p-value ≤0.05 was considered significant. The ethical approval was taken from Ethical Review Committee (ASRB) of Khyber Medical University Peshawar. The written and verbal consent was taken from every participant/parents, before starting data collection (taking radiograph and blood sample). Study objectives were clearly defined and explained to every participant.

RESULTS

The result indicates total 156 children were included with mean age 11.9±2.2, {97(62.2%) were being males and 59 (37.8%) were being females}. Detail categorization of age indicate that 35 (22.4%) were from 15 years of age group, followed by 29 (18.60%) in 10 years, 24 (15.40%) 9 years, 22 (14.10%) 12 years, 16 (10.30%) 14 years, 14 (9%) 11 years, 10 (6.4%) 13 years, 4 (2.5%) 9.5 years and 2 (1.3%) were from 10.5 years respectively; age category of the participants. (Figure-1)
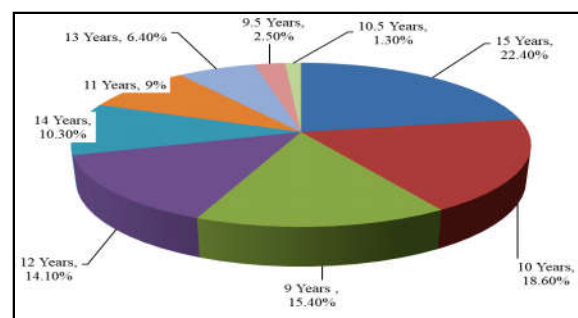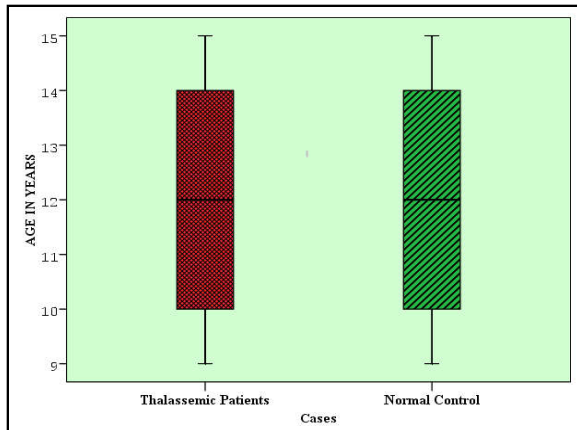

Figure-1: Age categorization of the participants

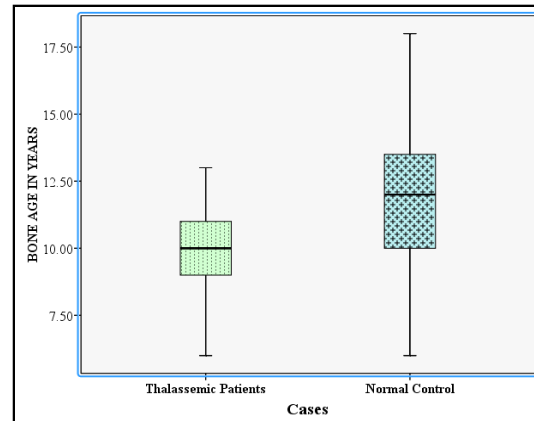Figure-2: Comparison of chronological age between two groups

Figure-3: Comparison of bone age among thalassaemic and normal children

Table-1: Comparison of bone age and chronological age among the study groups

Characteristics	Group A (Thalassaemic pts)	Group B (Normal control)	Confidence Interval (CI)	*p*-value
Chronological age (in yrs)	12.01±2.26	11.86±2.20	1.09-2.4	0.67
Bon age (in yrs)	9.9±1.6	11.7±2.5	0.55-0.85	0.0001

Table-2: Correlations among thalassaemic patients

	Pearson Correlation (r) and *p*- value	Number of erupted teeth	Bone age in years	Serum ferritin level in mcg/l	Growth hormone level in ng/ml
Number of erupted teeth	**(r)**	--	0.462(**)	0.032	0.051
	P-Value		0.00001	0.783	0.656
Bone age in years	**(r)**		--	1.145	0.244(*)
	p–Value			0.204	0.031

* Correlation is significant at the 0.05 level (2-tailed).

Table-3: Correlations among normal control

	Pearson Correlation (r) and *p*- value	Number of erupted teeth	Bone age in years	Serum ferritin level in mcg/l	Growth hormone level in ng/ml
Number of erupted teeth	(r)		0.559(**)	0.039	-0.043
	p-Value		0.00001	0.737	0.709
Bone age in years	**(r)**			.467(**)	0.118
	p-Value			.0001	0.302

**Correlation is significant at the 0.01 level (2-tailed).

Out of 156 participants 97 (62.2%) were being males and 59 (37.8%) were being females. The thalassaemic patients 49 (62.8%) male and 29 (37.2%) females and approximately similar ratio {48 (61.5%) male and 30 (38.5%) female. Out of 79 cases from Fatimid Hospital, 76 (96.20%) were thalassaemic patients and 3 (3.79 %) were normal. While the comparative groups were selected from Paediatric ward, Khyber teaching hospital, among 77 cases 2 (2.59%) were thalassaemic patients while 75 (97.40%) were normal.

Our study finding reveals that the mean chorological age among thalassaemic patients was 12.01±2.2 (ranged 9–15 years), where 50% were more than 12 years of age. Similarly, among control group the mean chronological age was 11.86±2.18 (range 9–15 years with median of 12.0 years), indicating the mean difference of 0.154 years (*p*=0.67) which is not significant and reveals a good matching during selection of control group as shown in (Figure-2)

When we compared the bone age between the two group the mean bone age among groups were significantly different from each other (*p*=0001). Result reveals that mean bone age among thalassaemic patients (9.9±1.6 years) were less as compared to control group (11.7±2.5) with mean difference of 1.7 years which indicate that the average bone age of thalassaemic patient needs more 1.7 years to acquire bone maturity required at a specific chronological age as shown in (Figure-3)

The overall mean chronological age among both the groups was similar. However, the mean bone age between the two groups was significantly different. The mean bone age was significantly lesser in thalassaemic patients as

compared to control group. (Table-1) Pearson's correlation analysis revealed that was strong correlation between erupt teeth and bone age (r=0.462, *p*=0.0001). (Table-2)

Among control group the bone age has significant correlation with erupted teeth (r=0 .559**, *p*=0.00001). Bone age was strongly associated with serum ferritin (r=0. .467**, *p*=0.0001), however the relationship with growth hormone was not significant (r = 0.161, *p*=0.302) as shown in Table-3.

DISCUSSION

The present study reveals that the mean bone age (9.9±1.6 years) of thalassemia patients was significantly different from control groups (11.7±2.5), (*p*=0001). The similar finding has been reported by other studies that despite of advancement in medical field, the survival of the patients improved. However, the growth failure and hypogonadism are the major problems in these patients in adolescence.[12] Studies have reported that the mean survival age of Indian thalassaemic patients have been increased due to modern therapies but it is becoming increasingly clear that as the patients approach the age of puberty, many develop growth retardation and pubertal failure.[13]

The overall mean chronological age among both of the group were approximately similar because it deliberately matched by researcher to prevent the biases. Furthermore, mean bone was significantly different i.e. the thalassaemic patients had lesser bone age as compare to that of normal children. The bone age of thalassaemic patient remains low as compare to the control group and it is found by majority of the studies.[12,14] This trend in the variation of bone age and chronological age is due to the bone mass density. The bone mass density among thalassaemic patients remains low as compared to the normal as predicted by other studies.[15] According to them low bone mass density is often present in patients with thalassemia, although recognized late, as in the present series. Early diagnosis should be done during childhood, in order to improve the quality of life in adulthood.[15] This delay in the maturation will result into delay in puberty of the individual. It has been shown that mean and SDS values for height, weight and sitting height of thalassaemic patients were significantly lower (*p*<0.001) than control cases of similar age. Height deficiency exceeded -2 SD in 18 patients and a delay in bone age (>2 SD below the mean) was observed in 36 out of 54 patients. Similarly, it was also observed that among 11 patients over 14 years, 9 showed delays in onset or progression of

puberty and 10 had growth retardation. These findings indicate that abnormal growth and delayed puberty are frequent in thalassemia approximately similar evidence were reported by other studies.[16,3,17]

CONCLUSION

Skeletal age assessment was found to be suboptimal along with chronological age in children and adolescents suffering from thalassemia. Hand wrist radiographs, growth hormones levels and dental eruption were used for the investigation. The manual methods for bone age determination are often imprecise, so automated methods should be adopted to improve accuracy and to have better plans for the treatment and quality of life of thalassaemic patients.

Conflict of Interest: None

AUTHOR'S CONTRIBUTION

AH helped in data collection, HI in study design, data interpretation and WA in critical review, final approval of manuscript.

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