Research Article

Effects of thalassaemia major on components of the craniofacial complex- a cephalometric study in Andhra Pradesh population

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ABSTRACT

The cephalometric study was conducted to evaluate the craniofacial effects of thalassaemia major on the Andhra Pradesh population. Methods: A total of 32 thalassaemic patients (23 male, 9 female) were selected from the Thalassaemia and Sickle Cell Society and 32 controls (19 male, 13 female) from schools of Hyderabad city to eliminate any bias on the ethnic background. All 64 lateral cephalograms were taken under standard conditions with teeth in occlusion and lips in a relaxed position. Forty – two linear and angular cephalometric parameters defining craniofacial morphology (22 skeletal, 13 dentoalveolar and 7 soft tissue) were selected. Results: Every patient with thalassaemia exhibited a skeletal base relationship of class II, accompanied by an average ANB angle of 4º. There was a significant increase in the length of the anterior cranial base. The length of the maxillary and mandibular base was significantly reduced, and the mandible appeared to be retruded in the face. Pronounced vertical growth was evident from linear and angular measurements. The dental deviations seen in thalassaemic patients were proclination, significant over-eruption of the maxillary anterior teeth and increased overjet. A marked increase in the convexity of the lower face, prominent upper lip, reduced nasolabial angle and increased inter-labial angle were evident from soft tissue measurements. Conclusions: The reduced length of the maxillary and mandibular base could be due to chronic anaemia which causes retardation of growth in thalassaemic patients. An increase in the anterior cranial base length resulted in the posterior positioning of the mandible and an increase in anterior facial height led to a skeletal class II pattern.

KEYWORDS: Anaemia; craniofacial growth; cephalometry; thalassaemia major.

INTRODUCTION

Thalassaemia is the most common monogenic disease worldwide. It is prevalent in some 60 nations with the most prevalence in the Mediterranean region, regions of North and West Africa, the Middle East, the Indian subcontinent, southern Far East, and southeastern Asia; together they compose the so-called "thalassaemia belt".[1]

Thalassaemia is a chronic, familial, hemolytic anaemia and is transmitted by autosomal co-dominated genes.[2] Based on clinical features, it is classified as homozygous, heterozygous or compound heterozygous. The heterozygous form is mild, with minimal clinical expression. The homozygous form exhibits the most severe clinical symptoms with marked orofacial defects. A less severe form is thalassaemia intermedia.[3, 4, 5, 6] Thalassaemia is called Cooley's anaemia since it was discovered by Dr Denton Cooley in 1927. It can also be referred to as Italian or Mediterranean anaemia since

it has its highest incidence in Mediterranean regions due to Mendelian inherited abnormality of haemoglobin synthesis. This condition is known by different names, including Mediterranean anaemia, Cooley's anaemia, hereditary elliptocytosis, and target oval-cell syndrome.[8] The disorder is produced due to failure to produce β globin chains and in addition ineffective erythropoiesis because of an excess of Alpha - globin chains which damage the cell membrane, resulting in cell lysis, an increased breakdown of cells, which leads to severe anaemia, hepatosplenomegaly and extra-medullary haematopoiesis with secondary skeletal deformity.[7, 8, 9]

The most common oral and facial appearance of the patient with thalassaemia is characterized by "Angle's Class II face" with prominent cheekbones, overgrowth of midface plus incisal prominence and spacing due to the expansion of marrow cavity and facial appearance known as "chipmunk" or "rodent" face coupled with mandibular corpus shortness, so that orthodontic treatment may be indicated.[9, 10]

Adelman proved that though orthodontic tooth movement was possible, severe vertical and lateral maxillary bone deformity could not be corrected by molar anchorage and extraoral headgear to retract the anterior maxillary arch and dentition.[11]

Quantitative assessments of the skeletal morphology of patients with thalassaemia major are rare. Therefore, the purpose of the present study was to conduct a cephalometric analysis of patients with thalassaemia major and to compare measurements with normal subjects of similar age to identify cephalometric and facial features of the Andhra Pradesh population with beta-thalassaemia major.

MATERIALS AND METHODS

This comparative study was conducted by the Department of Orthodontics and Dentofacial Orthopedics, Sri Sai College of Dental Surgery, Vikarabad, A.P in association with the Thalassaemia and Sickle Cell Society of Hyderabad, A.P to assess and compare cephalometric and facial characteristics in thalassaemic children and young adults. Ethical clearance was taken before the commencement of the study from the local ethical committee.

Out of 200 patients examined during a period of 6 months, 32 patients who were in the age group of 8-16 years were included in the study. All patients were in stable condition and no patient had received any orthodontic treatment. The control group consisted of 32 healthy children aged between 8-16 years from Noble High School, Dilsukhnagar, Hyderabad, A.P. The control group had no history of orthodontic treatment and did not present with craniofacial syndrome.

Both the sample and the control group were of the same ethnic origin. All 64 lateral cephalograms were taken under standardized conditions with the teeth in occlusion and lips in a relaxed position. Forty-two linear and angular cephalometric parameters defining craniofacial morphology (22 skeletal, 13 dentoalveolar, and 7 soft tissues) were selected.

Cephalometric values were measured by one author. For bilateral landmarks, the midpoint between the right and left images was used. Any discrepancies in landmark positions were resolved by mutual agreement between the three authors. Angular and linear measurements were recorded to the nearest 0.5° and 0.5 mm respectively and all radiographs were taken on the same machine.

The mean values of the cephalometric measurements of thalassemic patients and controls were compared using an independent t–test. A chi-square test was done to evaluate the significant difference concerning gender and age groups between the two groups. A p-value of < 0•05 was taken as the level of significance.

RESULTS

A composite analysis was done manually to assess the cephalometric characteristics. Forty – two linear and angular cephalometric parameters defining craniofacial morphology were analyzed, which were further divided into the following: -

1) Horizontal skeletal pattern
2) Vertical skeletal pattern
3) Dentition
4) Soft tissue features
5) Age and sex

Horizontal skeletal pattern

In general, measurements of the cranial base did not significantly differ from the control group. There was a statistically significant reduction of the maxillary base in the horizontal plane (ANS-PNS = 52.50 mm). SNA was in the normal range; however, statistically significant differences were found in relation to the mandible (SNB = 76.16o, Go-Me = 70.63 mm, N-Go-Me

= 76.84o, and SL = 50.78 mm). The mandible of the patients appeared to be smaller in size (Go-Me = 70.63 mm, and SL = 50.78 mm) and more retruded in the face (SNB = 76.16o). Relative to the control group, there was a class II skeletal pattern among thalassemic patients (ANB 4.50o vs. 3.09o) which was statistically significant (Table 1).

Vertical skeletal pattern

The decrease in upper anterior facial height (UAFH = 52.03mm) and increase in mandibular and maxillo-mandibular (ANS-PNS/Go-Gn = 32.72o vs. 23.56o) angles in the thalassemic group were statistically significant indicative of a severe vertical growth pattern. An insignificant difference was seen in the anterior and posterior facial heights in the thalassaemia group compared to the control. Likewise, there was no significant difference in the rotation of the palatal plane and the vertical height of the ramus of the mandible (Table 2).

Table 1. Comparison of skeletal angular measurement of both β-thalassaemia patients and normal subjects (8-16 years).

Skeletal Angular Measurement	Thalassaemia		Normal		p-value
	Mean	SD	Mean	SD	
SNA	80.75	3.04	82.28	3.81	0.08
SNB	76.16	3.91	79.16	3.37	0.002**
ANB	4.50	1.80	3.09	2.47	0.011**
N-S-Ar	123.78	4.50	124.44	5.09	0.587
S-Ar-Go	144.75	5.33	141.81	6.43	0.051
N-Go-Ar	56.66	13.22	53.25	5.59	0.184
N-Go-Me	76.84	12.07	70.69	3.73	0.008**
Ar-Go-Me	124.88	18.26	123.03	8.35	0.605
SN /GoGn	32.22	6.80	27.72	3.92	0.002**
SN/PNS-ANS	6.84	4.47	7.59	3.18	0.442
ANS-PNS/MP	32.72	9.74	23.56	4.64	<0.001**

Table 2.Comparison of skeletal linear measurements of β- thalassaemia patients and normal subjects (8-16 years).

Skeletal Linear Measurements	Thalassaemia		Normal		p-value
	Mean	SD	Mean	SD	
S-N	75.47	8.15	77.69	3.92	0.170
S-Ar	36.03	4.31	37.53	6.84	0.298
Ar-Go	45.56	7.95	49.28	10.01	0.105
Go-Me	70.63	6.34	76.47	6.85	0.001**
S-Go	77.87	10.09	79.84	14.57	0.532
N-Me	119.78	13.41	122.28	9.02	0.385
N-ANS	52.03	4.44	55.06	4.73	0.01**
ANS-Me	71.25	6.36	69.34	6.28	0.232
ANS-PNS	52.50	6.39	55.94	4.07	0.013**
SE	19.94	5.72	21.16	3.74	0.317
SL	50.78	10.93	58.84	8.50	0.002**

Dentition

The overjet was significantly increased in the thalassemic group (4.23 mm). The interincisal angle, maxillary and mandibular incisors' linear (I-NA and I-NB) and angular measurements (I-NA, I-SN for upper and I-NB, I-GoMe for lower incisors) were within the normal range. However, the linear distance of the maxillary incisor to the palatal plane (UI ⊥ANS-PNS) was recorded as extruded which was statistically significant (Table 3).

Soft tissue features

The thalassemic patients were found to exhibit a more convex profile than the control group (gl-Sn-Pog = 17.16o). Overall, the patients exhibited reduced interlabial angle (Sn-ls /li-Pog = 116.87o), reduced nasolabial angle (NLA= 89.22o) and prominent upper lips (ANS-PNS/ls-con = 137.41o) and differences were statistically significant (Table 4).

Table 3. Comparison of sagittal and vertical dentoalveolar linear and angular measurements of both β – thalassaemia patients and normal subjects (8-16 years)

Sagittal and Vertical Dentoalveolar Measurement (Angular and linear)	Thalassaemia		Normal		p-value
	Mean	SD	Mean	SD	
I-NA	30.63	15.53	28.09	5.37	0.387
I-SN	104.78	13.92	109.38	8.70	0.118
I-NB	37.00	14.45	34.28	5.74	0.326
I- GoMe	101.66	7.64	104.09	5.68	0.152
I / I	112.47	19.82	115.44	11.08	0.462
UM ⊥ ANS-PNS	22.52	2.53	23.03	3.02	0.462
UI ⊥ ANS-PNS	32.75	3.32	30.34	3.49	0.006**
LM ⊥GoMe	33.78	3.30	33.91	2.91	0.873
LI ⊥ GoMe	42.59	7.51	43.78	3.21	0.414
I-NA	8.28	2.74	8.69	3.50	0.607
I-NB	8.78	2.76	8.50	2.21	0.654
OVERJET	4.23	1.75	2.94	1.56	0.003**
OVERBITE	4.34	1.84	4.13	1.72	0.625

Table 4. Comparison of sagittal and vertical soft tissue linear and angular measurements of both β – thalassaemia patients and normal subjects (8-16 years).

Sagittal and Vertical Soft tissue Measurement (Angular and linear)	Thalassaemia		Normal		p-value
	Mean	SD	Mean	SD	
gl-sn-pg	17.16	4.03	13.63	6.08	0.008**
sn-ls / li-pg	116.87	21.91	131.22	14.09	0.003**
NLA	89.22	10.06	98.25	11.35	0.001**
ANS-PNS / ls-con	137.41	8.75	128.19	14.02	0.002**
ANS-PNS / li-con	23.75	12.69	23.25	14.98	0.886
sn-pg ⊥ ls	10.56	14.28	7.16	2.00	0.186
Sn-pg ⊥ li	7.38	2.89	7.31	2.55	0.927

Age and sex

The age and sex of both groups were compared using the chi-square test. In the thalassaemia group, females were 28.1% and males were 71.9% while in the control group, 40.6% were females and 59.4% were males. The difference was not statistically significant. In the 8-11 age group, 46.7% of children had β–thalassaemia and 56.3% were unaffected whereas, in the 12-16 age group, 53.3% of children had β–thalassaemia and 43.8% were unaffected (Table 5).

Table 5. Comparison of sex and age of both β – thalassaemia patients and normal subjects (8-16 years).

Group		Thalassaemia		Normal		p-value
		N	%	N	%	
Sex	F	9	28.1%	13	40.6%	0.292 NS
	M	23	71.9%	19	59.4%	
Age	8-11	14	46.7%	18	56.3%	0.45 NS
	12-16	16	53.3%	14	43.8%	

DISCUSSION

The present aimed to evaluate craniofacial abnormalities by means of cephalometric measurements in a group of subjects suffering from β – thalassaemia major and compared with healthy individuals of the same age group (8-16 years). These subjects were all diagnosed with thalassaemia within one to two years after birth and were receiving blood transfusions regularly including chelation protocol. The control subjects belonging to the same age group were enrolled to eliminate any bias on the ethnic background. Bassimitci et al.[2] argued that matching thalassemic patients with normal subjects based on skeletal age is not a reliable method, but they suggested no alternatives.

Little is known about the cephalometric characteristics and the possibility of orthodontic treatment in thalassaemic patients. Successful surgical correction and osseointegrated implant surgery of the maxilla have been reported in a few cases.[5]

The evaluation of the horizontal skeletal pattern demonstrated an increase in the length of the anterior cranial base in thalassaemic patients compared to the control group which was not significant and is in line with a study conducted by F Amini et al.[1] However, the length of the maxillary base was reduced in thalassaemic patients by 3.40 mm which was statistically significant. This finding is not in agreement with F Amini et al.[1] and Abu Alhaija et al.[3] who stated that the maxilla was normal. However, the mandible of the thalassaemic patients appeared to be retruded in the face with an SNB difference of 3º and smaller in size with Go-Me reduced by 5.16 mm. The possible reasons could be chronic anaemia, irregular and insufficient transfusions or maxillary overgrowth preventing the growth of the mandible and general growth retardation due to various above-mentioned factors.

The ANB angle was greater by 1.41º among the thalassaemic patients compared to the control group and the difference was statistically significant. The development of the "Class II pattern faces" can be attributed to the fact that the mandible grows slower than the maxilla and therefore is being blocked by the excessive vertical maxillary growth and also because the maxilla completely encapsulates the mandible. Defective growth and lack of pubertal development are probably strictly correlated; the complex interactions between androgens, estradiol, and somatomedin-C have been recently reviewed.12 Evidence for retardation of growth data showed body growth was satisfactory but bone age was generally retarded, more so in boys than in girls. Other studies have reported that normal growth was seen in children with haemoglobin levels above 8g/dl.[13]

The vertical skeletal evaluation of thalassaemic patients exhibited an increase in middle anterior facial height by 3.03 mm, lower gonial angle by 5.05º, mandibular plane angle by 5.46º and basal plane angle by 9.16º which were statistically significant and indicated a vertical growth pattern. The study conducted by F Amini et al[1] found an increase in lower anterior facial height among thalassaemic patients, but in the present study, middle facial height was increased which might be because

of the expansion of bone marrow spaces in maxillae. The anti-clockwise rotation of the mandible or increase in basal plane angle was statistically significant. Various explanations for this pronounced vertical growth direction have been reported such as muscular weakness, mouth breathing pattern 14, vertical descent of the posterior maxilla (due to enlargement of the maxillary marrow spaces) and probably a deficient ramus and condylar growth.

The examination of dentition showed that the maxillary incisors were extruded by 2.41mm in the thalassemic patients than that of controls which was statistically significant. There was also a statistically significant greater overjet by 1.29 mm in the thalassemic patients. Bassimitci et al.[2] reported an increased overbite in thalassaemic patients, but it was not statistically significant. The dentoalveolar compensation in the vertical plane (average overbite) was seen in the form of overeruption of the upper and lower incisors similar to previously published studies. In addition, the tooth-crown size and tooth length were significantly smaller in thalassemic patients.[15]

This study found statistically significant increase in facial convexity, inter labial angle and prominence of upper lip but reduction in nasolabial angle in the thalassemic patient than controls. The smaller chin was accompanied by more prominent lips which reduces the interlabial angle. Interestingly, Abu Alhaija et al.[3] in an investigation reported that the thalassaemic patients had a smaller tongue size, shorter soft palate, and smaller upper, and middle pharyngeal lengths. Whether these alterations of the uvulo-glosso-pharyngeal dimensions are the direct causes of skeletal alterations is unknown.[16]

It has been stated that the effects of thalassaemia on bones depend on the severity of the anaemia, the patient's age, the duration of the clinical symptoms and the timing of both therapeutic blood transfusion and splenectomy.[17] The transfusion therapy may diminish or, indeed, prevent the development of bony abnormalities in growing patients.[18,19] Based on the results of this study it could be argued that subjects who are on regular transfusions have no gross craniofacial deformities. The various factors causing growth retardation in β-thalassaemia could be a possible cause for the narrower and shorter maxilla and mandible.

CONCLUSION

Children with thalassaemia major, irrespective of ethnic background, exhibited a distinct craniofacial morphology characterized by a class II skeletal pattern with a strong vertical component of growth. The literature records only skeletal overgrowth of the maxilla and zygoma. However, from the results of the present study, it can be concluded that as a result of anaemia, the expansion of marrow spaces and growth retardation of the maxilla and mandible leads to the development of facial dysmorphology

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