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The Effect of Beta Thalassemia Major on Anterior Cranial Base in Cephalometric Analysis
(Systematic Literature Review)

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Abstract

Background: Thalassemia is a group of hemolytic diseases caused by genetic disorders resulting from a decrease in the synthesis of the alpha or beta chains of hemoglobin (Hb). A particular craniofacial cephalometric picture is found in the form of mild skeletal class II clinical manifestations. The anterior cranial base becomes a benchmark or reference sector in the measurement of dentofacial structures on cephalometric radiographs because it is considered relatively stable throughout craniofacial growth. **Objective**: The purpose of this systematic literature review was to determine the effect of beta thalassemia major on the length of the anterior cranial base observed through cephalometric analysis. **Methods**: References were selected using the PubMed, Science Direct, and Google Scholar databases published from January 2007 to December 2021. The complete articles that met the inclusion and exclusion criteria were then assessed using the Critical Appraisal Skills Program bias assessment and summarized to obtain demographic data and the length of the patient's anterior cranial base in the journal. **Results**: This systematic literature review succeeded in synthesizing 6 journals consisting of case-control studies with low bias assessment results in 4 journals and moderate bias assessment in 2 journals. All journals in this systematic literature review stated that the length of the anterior cranial base in patients with beta thalassemia major was not much different from the control group seen in cephalometric analysis. **Conclusion**: There is no effect on the length of the anterior cranial base in patients with beta thalassemia major based on measurements on cephalometric analysis.

Keywords: anterior cranial base; beta thalassemia major; cephalometric radiograph

Introduction

Beta thalassemia major is an autosomal recessive disorder due to homozygous mutations (beta-zero thalassemia) of the beta-globin gene, which causes reduced or no production of beta-globin chains at all.[1,2] According to the world population, between 300,000 and 400,000 babies are born with serious hemoglobin disorders each year, with up to 23,000 babies suffering from beta thalassemia major.[3] Indonesia is one of the countries in the world's thalassemia belt, in 2018 KEMENKES data found that the frequency of the beta thalassemia gene ranged from 3-10%.[4]

The typical clinical picture in patients with thalassemia beta major is a prominent frontal and parietal bone, known as frontal bossing; the zygomatic bone also protrudes so that the nasal bridge is compressed and may also widen.[5,6,7] Maxillary protrusion results in orbital

hypertelorism, mandibular overbite, and class 2 malocclusion, known as "cooley faces" or "chipmunk faces".[5,8] The typical radiographic appearance is the camelback shape, which is an asymmetry in the calvarium that makes it look hollow, and trabeculae with bone marrow hyperplasia that give a very characteristic "hair-on-end" appearance.[5,9,10]

As an important factor in improving quality of life and self-confidence, this malocclusion condition necessitates orthodontic treatment.[11] Cephalometric radiographic analysis is one of the supporting examinations needed to study craniofacial morphology in orthodontic treatment. The anterior cranial base is a reference plane in measuring dentofacial structures on cephalometric radiographs because it is considered relatively stable throughout craniofacial growth.[12]

Methods

This type of research was carried out in the form of a systematic literature review with qualitative analysis. The type of study used is case control. The population studied was beta thalassemia sufferers aged at least 7 years with various genders and races. The comparison used was the control group (non-beta thalassemia patients). The outcome of this systematic literature review is the difference in anterior cranial base length on cephalometric radiographs. The settings used are hospitals or other health facilities in Indonesia and abroad.

The journal databases to be used are PubMed, Google Scholar, and Science Direct. The keywords and controlled vocabulary used are listed in Table 1. The data search was carried out using a combination of keywords and Boolean operators from the Population, Comparison, and Outcome (PCO) inclusion criteria, which can be seen in Table 2. The libraries used contain journals published in English and Indonesian in the last 15 years.

Tabel 1. Data Search Strategy

Inclusion Criteria	Population and setting	Intervention/ Exposure	Comparison	Outcome
Keyword	Children1 Adolescent2 Adult3 Beta Thalassemia[4]	-	Control group	Anterior Cranial base[1] Cephalometric[2]

Natural Language	1: Kid, Prepubescent, School-aged 2: Juvenile, Teenager, Youngster, Teen, Youth, Pubescent 3: Person, Man, Men, Woman, Women, Grown-up	-	-	-
Controlled Vocabulary	1: Child 2: Adolescent, Teenager, Youth 4: Beta thalassemia major, Beta thalassemia minor, HbE beta thalassemia, Transfusion-dependent beta thalassemia	-	-	2:Lateral cephalometric, Conventional cephalometric, Digital cephalometric, Cone-beam computed tomography cephalometric, Computed tomography cephalometric
Exclusion Criteria	**Population and setting**	**Intervention/ Exposure**	**Comparison**	**Outcome**
Keyword	Congenital Abnormality[1] Toddler (<7 y.o.)[2] Orthodontic treatmet[3] Craniofacial deformity[4]	-	-	Poor quality of cephalograms
Natural Language	1: Congenital anomaly, congenital disorder. 2: Infant, tot	-	-	-
Controlled Vocabulary	2: Preschool 3: Removable orthodontic appliances, Semi-fixed orthodontics appliances, Fixed orthodontic appliances 4: Acquired craniofacial deformity, Congenital craniofacial deformity	-	-	-

Tabel 2. Database Based Search Strategy

Database	Search Strategy
Pubmed	*Children OR Kid OR Prepubescent OR School-aged OR Adolescent OR Juvenile OR Teenager OR Youngster OR Teen OR Youth OR Pubescent OR Adult OR Person OR Man OR Men OR Woman OR Women OR Grown-up) AND (Beta thalassemia OR Beta thalassemia major OR Beta thalassemia minor OR HbE beta thalassemia OR Transfusion-dependent beta thalassemia) AND (Anterior Cranial Base) AND*

	(Cephalometric OR Lateral cephalometric OR Conventional cephalometric OR Digital cephalometric OR Cone-beam computed tomography cephalometric OR Computed tomography cephalometric)
Science Direct	*Beta thalassemia AND Anterior Cranial Base AND Cephalometric*
Google Scholar	*Beta thalassemia AND Anterior Cranial base AND Cephalometric*

Table 3. Summary of the journals analyzed

			Demographic Data				
Journal Title	**Researcher, Year of Publication**	**Types of Research**	**Category**	**Average Age (years)**	**Gender (M,F)**	**Number of Subjects**	**Mean Anterior Cranial Base Length ± Standard Deviation**
Craniofacial parameters of Syrian children with b-thalassemia major[13]	Takriti *et al*, 2011[13]	*Case-control*	THC	9,46 9,44	28,23 26,24	51 50	68.12 ± 3.26 67.72 ± 2.65
A cephalometric study on craniofacial morphology of Iranian children with betathalassemia major[8]	Amini *et al*, 2007[8]	*Case-control*	THC	10,4 10,01	18,12 -	30 30	67.95 ± 1.58 67.99 ± 3.76
Skeletal dentoalveolar and soft tissue effects of β thalassemia major[14]	Akkurt *et al*, 2014[14]	*Case-control*	THC	13,7 13,9	12,13 22,23	25 45	62.50 ± 4.05 64.04 ± 2.86
Cephalometric Aspect of Thalassemia Children in the Indian Subcontient[15]	Samba *et al*, 2018[15]	*Case-control*	THC	td (8-16) (8-16)	- -	31 41	68.40 ± 2.93 69.30 ± 3.81

Orofacial bone complications in thalassemic children associated with cephalometric evaluation[16]	Tutanc *et al*, 2017[16]	*Case-control*	TH C	14.07 12.57	9,17 14,16	26 30	63.69 ± 3.6 62.6 ± 3.14
The efficiency of orthodontic treatment of class ii malocclusion in children with b-thalassemia major[17]	Shadlinskaya *et al*, 2021[17].	*Case-control*	TH C	12.2 11.8	- -	26 23	67,78±3,83 68,04±2,76

*p-value< 0.05, **p-value= 0.007, ***p-value≤0.001, C: Control, TH: Thalassemia, M: Male, F: Female, td: No data.

Discussions

This systematic literature review uses case-control journals by involving male and female subjects with a minimum age of 7 years, which is according to the inclusion criteria. There is only one journal (Akkurt et al.) that has a proportion of subjects between men and women with a difference of one, and two journals (Takriti et al. and Tutanc et al.) with a difference in subjects between men and women of more than four. The number of male and female subjects was not mentioned in the other three journals. The length of the anterior cranial base can be affected by sex, with a greater value in males than females, so the proportion of males and females in the study should be the same.[18] In three journals (Amini et al., Samba et al., and Shadlinskaya et al.), it is not known exactly how the age distribution of the patients studied was because they only mentioned the age range of the patients studied and did not mention the average age. It is important to know the age distribution of the patients because the measurement results of the anterior cranial base length in certain age groups differ from those in other age groups.[18,19] The subjects used must also be aged 7 years and over because the length of the anterior cranial base has finished growing at the age of 7 years, so the readiness of the anterior cranial base of all subjects is the same.[12]

All the journals discussed focus on patients with beta-major thalassemia, and anterior cranial base length measurements were performed digitally through cephalometric radiographic

analysis. There were three journals that measured the length of the anterior cranial base twice, two of which (Takriti et al. and Akkurt et al.) were measured by one person at different times, and one journal (Amini et al.) was measured by two people. different, while the repetition of measurements is not explained in the other three journals. The more measurement experiments that are performed, the more reliable the test results become.[20] Researchers need to consider these limitations in determining research methods regarding the effect of beta thalassemia major on anterior cranial base length so that further research can be more specific.

The length of the anterior cranial base can be influenced by several factors, including brain development, genetics, gender, nutrition, age, and race.[18,21] The results of all journals used in the systematic literature review are the same, namely that there is no significant difference between patients with thalassemia beta major and the control group reviewed through cephalometric analysis.

The length of the anterior cranial base is affected by sex. In males, the anterior cranial base is longer than in females.[18,19,22] This is in line with a study conducted by Takriti et al., which found significant differences in the length of the anterior cranial base between males and females. The male head is 2% larger than the female head, and the male brain is 10% larger than the female brain. The male brain is larger due to the greater male muscle mass and body size, so it requires more neurons to control it. This is what causes the size of the cranial base in males to be larger than that in females.[23,24,25]

Cranial growth goes hand in hand with brain development, which causes brain development to control the average growth, shape of the cranial, and final size of the cranial; therefore, the brain is related to cranial base morphogenesis.[23,26] Brain volume at the age of 2 years has reached 80%, so to make room for the brain, the cranial base must grow rapidly to adapt to brain volume.[21,25] As the brain grows, it stretches the sutures, signaling the sutures to make new bone. The sutures allow the cranial base to expand and create sufficient space for the brain.[26]

The length of the anterior cranial base is also influenced by genetics, so there are variations between races.[18.22] The morphology of the size of the anterior cranial base varies between races, including the Mongolian race, which has a more brachycephalic craniofacial shape than the Caucasoid race, and the Negroid race, which has a more dolicocephalic craniofacial shape.[18,27] Anterior cranial base measurement should be measured in the same race

because individuals in one race have the same genetic ancestry, so there are no population differences.[28]

Conclusion

Based on measurements on cephalometric radiographs, there is no effect on the length of the anterior cranial base in patients with thalassemia beta major.

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