Craniofacial Characteristics of Thalassemia Major Patients

Talasemi Major'lü Hastaların Kraniofasiyal Özellikleri

Sacide Karakas[1], Ayfer Metin Tellioglu[1], Mehmet Bilgin[2], Imran Kurt Omurlu[3], Sercin Caliskan[2], Salih Coskun[4]

ABSTRACT

Objective: Thalassemias major are the most common autosomal recessive disorders; they are characterized by anomalies in the synthesis of the beta chains of hemoglobin and are often associated with varying degrees of craniofacial anomalies. The purpose of this study was to evaluate the craniofacial dimensions of β-thalassemia patients and to identify differences by comparing them to those of a control group.

Materials and Methods: The study comprised 43 thalassemia major patients and 26 age- and sex-matched healthy control subjects. Anthropometric measurements were performed in six different craniofacial regions (head, face, nose, mouth, eyes, and ears); a total of 23 craniofacial variables were measured.

Results: Craniofacial measurements in the regions of the face, nose, lips and mouth, and ears in the thalassemia major patient group yielded statistically significant differences compared to those in the control group ($p<0.05$). However, no statistically significant differences were observed in the measurements of the head and eye regions.

Conclusion: The study increased our understanding of the craniofacial anatomy of thalassemia major patients and enabled us to obtain quantitative results.

Keywords: Thalassemia major, craniofacial measurements, Turkey

ÖZ

Amaç: Talasemi major; otozomal resesif kalıtım paterni gösteren, hemoglobin beta zincirinin sentezinde bozukluklar ile karakterize ve genellikle değişen derecelerde kraniyofasiyal anomalilerin eşlik ettiği bir hastalıktır. Bu çalışmanın amacı, talasemi major' hastalarının kraniofasial boyutlarını değerlendirmek ve kontrol grubuna göre farklılıkları tespit etmektir.

Gereç ve Yöntem: Çalışmamız; 43 Talasemi Major'lü hasta ve aynı yaş ve cinsiyet gruplarından eşleşme ile seçilen 26 sağlıklı kontrol üzerinde yapıldı. Antropometrik ölçümler altı farklı kraniofasiyal bölgeden (baş, yüz, burun, ağız, göz ve kulak bölgeleri) alındı ve toplam 23 ölçüm yapıldı.

Bulgular: Yüz, burun, ağız ve kulak bölgelerinde yapılan ölçümler açısından olgu ve kontrol grupları arasında istatistiksel olarak anlamlı farklılıklar bulundu ($p<0.05$). Baş ve göz bölgesi ölçümleri bakımından istatistiksel olarak anlamlı fark saptanmadı($p>0,05$).

Sonuç: Çalışmamız Talasemi major'lu olguların kraniofasiyal anatomisini anlamamızı ve kantitatif sonuçlar elde etmemizi sağlamıştır.

Anahtar Kelimeler: Talasemi major, kraniyofasiyal ölçümler, Türkiye

[1]Department of Anatomy, Adnan Menderes University School of Medicine, Aydın, Turkey
[2]Department of Biophysics, Adnan Menderes University School of Medicine, Aydın, Turkey
[3]Department of Biostatistics, Adnan Menderes University School of Medicine, Aydın, Turkey
[4]Department of Genetic, Dicle University School of Medicine, Diyarbakır, Turkey

Received: January 29, 2015
Accepted: January 18, 2016

Correspondence to: Sacide Karakas

E-mail: skarakas@adu.edu.tr

DOI 10.5152/eurasianjmed.2016.150013

Introduction

Thalassemia is an inherited blood disease demonstrating clinical differences, resulting in hypo chromic microcytic anemia, and is characterized by the lack or deficient production of alpha or beta globin protein chains. Thalassemia major is a term used to describe the condition of homozygote or combined heterozygote beta thalassemia patients.

Thalassemia major are a group of hereditary blood disorders characterized by absent or reduced β-globin chain synthesis that results in hypochromic microcytic anemia [1]. Thalassemia major, also known as "Cooley's anemia" or "Mediterranean anemia," is the most severe form of beta-thalassemia; thalassemia major patients are homozygotes or compound heterozygotes for $beta^0$ or $beta^+$ genes [2].

The clinical onset of disease symptoms occurs in the last six months of the first age. Patients present with severe and progressive hemolytic anemia. Clinical findings include serious anemia, ineffective erythrocyte production, extramedullary hematopoiesis, and overaccumulation of iron as a result of blood transfusions. Treatment of the disease requires blood transfusions at regular intervals to prevent heart failure associated with profound anemia. Hypertrophy associated with excess erythropoiesis of the bone marrow and the extramedullary region is observed in patients who receive insufficient transfusions [2, 3]. The orofacial symptoms of thalassemia are due to bone changes associated with ineffective erythropoiesis. The bones become thinner, and pathological fractures may occur. Changes in facial and cranial bones have been identified as the overexpansion of the bone marrow results in a typical facial appearance. The craniofacial features of thalassemia major patients include larger cheekbones, a rodent or "squirrel-like" face, a depressed nasal bridge, and a protruding maxilla. The deformations of the "squirrel-like" face are attributed to multi-directional growth, covering the maxillary region in particular, and dental protrusion involving the affected teeth [4-6]. Features characterized by prominent frontal and parietal bones, a collapsed nasal bridge, depression of the zygomaticus, and upward-slanted eyes are defined as a slightly mongoloid facial deformity in some patients [4, 6].

Thalassemia major is widespread throughout Turkey; the frequency of carriers of the disease is 2.1%, and this rate increases to 10% in some areas. In Turkey, the number of homozygote β-thalassemia patients is estimated to be 4000, while the number of carriers of thalassemia major is estimated to be 1,300,000 [7-9].

Anthropometry is a method used in the measurement of compositions of bones, muscles, and fatty tissues in the human body [10]. Craniofacial anthropometry involves the measurement of the skull and face [11]. The numerical identification of the present disproportion of a morphological facial deformity is the main purpose of these measurements [11, 12]. Craniofacial anthropometry is a useful numerical identification method that assists clinicians to identify deformities and helps surgeons at the stage of reconstructive intervention [13].

In this study, our main purpose was to evaluate the craniofacial dimensions of thalassemia major patients and to identify differences by comparing them to those of a control group of comparable age, sex, and ethnicity.

Table 1. Definitive statistics of the patient group

Measurements	Mean±SD or median (25th–75th percentile)	Min	Max
Circumference of head (cm)	53.09±2.8	48.0	60.5
eu-eu (mm)	14.76±0.76	13.30	16.50
ex-ex (mm)	94.07±7.9	77.40	107.10
en-en (mm)	30.85±3.19	23.1	36.8
zy-zy (mm)	106.0 (97.8–115.0)	13.8	128.5
ps-pi (mm)	31.11±4.22	23.2	40.1
en-ex (right) (mm)	32.80±2.9	26.3	38.8
en-ex (left) (mm)	32.76±2.9	26.3	38.4
al-al (mm)	26.15±3.9	20.7	35.4
ch-ch (mm)	43.31±6.26	22.0	55.5
n-gn (mm)	103.9 (96.1–116.7)	75.3	131.3
n-sn (mm)	52.3 (47.4–58.6)	34.3	77.6
n-sto (mm)	69.57±9.46	49.5	93.4
sn-sto (mm)	19.39±3.66	10.60	30.3
sto-is (mm)	17.88±3.32	10.7	32.6
t-sn (mm)	117.97±10.25	97.6	143.0
t-gn (mm)	128.35±11.51	107.8	147.6
sn-prn (mm)	18.7 (16.8–20.3)	12.0	38.7
mf-mf (mm)	20.91±2.32	15.7	27.5
pra-pa right (mm)	37.2 (35.6–38.6)	30.9	44.8
pra-pa left (mm)	37.3 (35.6–38.8)	30.7	43.9
sa-sba right (mm)	64.0 (59.8–67.3)	54.4	74.3
sa-sba left (mm)	64.2 (60.1–67.2)	54.1	74.1

Head width (eu-eu); biorbital width (ex-ex); intercanthal width (en-en); face width (zy-zy); palpebral fissure height (ps-pi); palpebral fissure length (en-ex); nose width (al-al); mouth width (ch-ch); face height (n-gn); nose height (n-sn); upper face height (n-sto); upper lip height (sn-sto); lower lip height (sto-is); midface depth (t-sn); lower face depth (t-gn); nasal tip protrusion (sn-prn); nasal root width (mf-mf); ear width (pra-pa); and ear length (sa-sba); Min: minimum; max: maxium

Materials and Methods

Subjects

Forty-three thalassemia major patients (22 females and 21 males) aged between 4 and 36 years from the pediatric or hematology clinics of state hospitals in Aydin, Turkey were included in the study group. The control group comprised 26 subjects (12 females and 14 males) with matched ages, ethnicities, and social backgrounds. All controls were healthy subjects with no history of craniofacial abnormalities or facial surgery.

Ethics approval

The study protocol was approved by the Human Ethics Committee of Adnan Menderes University and from Ministry of Health, Turkey. All subjects or their parents/guardians were informed about the study and signed the appropriate consent forms complying with the regulations of the Ethical Committee.

Craniofacial anthropometric measurements

All subjects or their parents were informed about the craniofacial anthropometric measurements. A total of 23 anthropometric measurements in six craniofacial regions (two on the head, five on the face, four on the nose, five on the eyes, three on the lips and mouth, and four on the ears) per subject were performed using calipers. Briefly, all landmarks were labeled on each subject's face with a surgical marking pen. Linear measurements were taken directly on the labeled faces of the subjects while applying minimal pressure to the soft tissues, according to the Farkas method [14].

The 23 craniofacial measurements at the six craniofacial regions are named as follows: head: head circumference and head width (eu-eu); face: face width (zy-zy), face height (n-gn), upper face height (n-sto), midface depth (t-sn), and lower face depth (t-gn); nose: nose width (al-al), nose height (n-sn), nasal root width (mf-mf), and nasal tip protrusion (sn-prn); eyes: biorbital width (ex-ex), intercanthal width (en-en),

Table 2. Comparison of head measurements between the patient group and the control group

	Male			Female			All groups		
Measurement	Patient	Control	p	Patient	Control	p	Patient	Control	p
Head circumference (cm)	53.6±2.3	55.2±2.6	0.071	53.5 (49.0–55.0)	54 (53–54.8)	0.635	53.1±2.8	54.4±2.4	0.051
eu-eu (mm)	14.8±0.7	14.7±2.6	0.111	14.7±0.8	14.9±0.8	0.692	14.8±0.7	14.7±0.8	0.150

Head width (eu-eu)

Table 3. Comparison of facial measurements between the patient group and the control group

	Male			Female			All groups		
Measurement (mm)	Patient	Control	p	Patient	Control	p	Patient	Control	p
zy-zy	106.0 (94.4-112.7)	108.9 (90-113.3)	0.763	107.3 (100.5-117.3)	103.1 (96.8-105.8)	0.074	106.0 (97.8-115.0)	104.9 (95.7-110.1)	0.213
n-gn	106.6 (98.3-113.4)	120.5 (109.9-126.1)	0.016	104.9±14.8	109.7±9.8	0.329	103.9 (96.1-116.7)	119.1 (104.3-123.1)	0.014
n-sto	69.7 (62.5-77.2)	80.9 (76.27-82.15)	0.009	69.3±10.0	71.6±6.9	0.471	69.57±9.4	75.2±7.9	0.014
t-sn	120.2±9.1	124.7±10.7	0.194	115.6 (110.4-120.0)	116.8 (109.8-120.3)	0.815	117.9±10.2	119.4±12.4	0.602
t-gn	130.1±10.8	140.8±11.7	0.010	126.6±12.08	128.1±13.0	0.728	128.3±11.5	134.9±13.6	0.035

Face width (zy-zy); face height (n-gn); upper face height (n-sto); midface depth (t-sn); and lower face depth (t-gn)

Table 4. Comparison of nasal region measurements between the patient group and the control group

	Male			Female			All groups		
Measurement (mm)	Patient	Control	p	Patient	Control	p	Patient	Control	p
al-al	26.7±4.2	25.6±3.6	0.469	25.6±3.6	22.37±1.74	0.006*	26.15±3.9	24.14±3.3	0.032
n-sn	52.8 (47.4-57.7)	64.7 (61.67-67.2)	0.003	52.08±8.76	58.1±8.38	0.061	52.3 (47.4-58.6)	63.5 (54.47-66.27)	<0.05
mf-mf	20.90±2.50	19.88±1.69	0.190	20.92±2.20	18.82±2.09	0.011*	20.91±2.32	19.39±1.9	0.007
sn-prn	19.2 (15.9-20.7)	21.55 (20.9-24.02)	0.002	18.9 (14.7-20.2)	20.6 (19.3-22.8)	0.007	18.7 (16.8-20.3)	21.55 (19.47-23.92)	<0.05

Nose width (al-al), nose height (n-sn), nasal root width (mf-mf), and nasal tip protrusion (sn-prn)

palpebral fissure height (ps-pi), and palpebral fissure length (en-ex); lips and mouth: mouth width (ch-ch), lower lip height (sto-is), and upper lip height (sn-sto); and ears: ear width (pra-pa) and ear length (sa-sba) [14].

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 12.0 (SPSS Inc.; Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test the normal distribution of the variables (p>0.05). Quantitative data without normal distributions were analyzed using the Mann–Whitney U test and were expressed as median and percentile. Data with normal distributions were analyzed using Student's t test and were expressed as mean and standard deviation (p<0.05, statistically significant).

Results

The times required to perform the craniofacial measurements were approximately equal, averaging approximately 30 minutes per subject. Definitive statistics of the patient groups are given in Table 1. Comparisons of the craniofacial measurements in each region between the patient and control groups are shown in Tables 2 to 7. There was a difference in head circumference between the patients and control subjects; however, it was not statistically significant (p=0.051, Table 2). A general evaluation of the patients revealed that their face heights (n-gn), upper face lengths (n-sto), and lower face depths (t-gn) were significantly smaller than those in the control group (p<0.05, Table 3). These facial measurements in male patients were also significantly smaller than those in the control group; however, there were no significant differences in the facial measurements between the female subjects (p>0.05, Table 3). All patients' measurements in the nasal region were significantly different from the controls (Table 4). The nose height (n-sn) and nasal tip protrusion (sn-prn) measurements in males were significantly smaller than those of the controls. The nasal root width (mf-mf) and nose width (al-al) measurements in female patients were significantly larger than those of the controls; however, the nasal tip protrusion (sn-prn) measurements were significantly smaller than those of the controls (Table 4). Evaluation of the eye region measurements between the patient and control groups did not yield statistical significance (p>0.05, Table 5). The mouth widths (ch-ch) of all the patients were significantly smaller than the mouth widths of the controls (p<0.05). The upper lip heights (sn-sto) of all the patients were significantly larger than those of the controls (p<0.05); however, the lower lip heights (sto-is) were not significantly different from those of the controls (Table 6). The right and left ear widths of both male and female patients were not significantly different from those of the controls. However, the right and left ear widths of the entire patient group were measured to be smaller than those

Table 5. Comparison of the eye region between the patient group and the control group

	Male			Female			All groups		
Measurement (mm)	Patient	Control	p	Patient	Control	p	Patient	Control	p
ex-ex	95.1 (88.3-101.0)	11.4 (88.5-104.3)	0.274	93.64±7.35	91.85±4.74	0.455	94.07±7.9	94.88±7.45	0.674
en-en	31.39±2.86	15.22±0.84	0.717	30.36±3.46	30±2.59	0.753	30.85±3.19	30.51±3.35	0.683
ps-pi	30.27±4.46	29.25±2.61	0.446	31.91±3.92	30.24±3.89	0.241	31.11±4.22	29.7±3.23	0.150
en-ex (right)	33.17±3.14	33.52±3.01	0.740	32.44±2.64	31.57±2.01	0.328	32.80±2.9	32.62±2.73	0.806
en-ex (left)	33.10±3.05	33.47±3.04	0.725	32.43±2.74	31.61±1.9	0.365	32.76±2.9	32.61±2.7	0.838

Biorbital width (ex-ex), intercanthal width (en-en), palpebral fissure height (ps-pi), and palpebral fissure length (en-ex)

Table 6. Comparison of the measurements of the lip and mouth region between the patient group and the control group

	Male			Female			All groups		
Measurement (mm)	Patient	Control	p	Patient	Control	p	Patient	Control	p
ch-ch	45.22±5.08	47.55±7.41	0.276	41.5±6.84	45.74±3.56	0.055	43.31±6.26	46.71±5.92	0.029*
sto-is	18.6±3.95	18.26±2.54	0.781	17.20±2.48	16.6±2.5	0.510	17.88±3.32	17.5±2.61	0.615
sn-sto	18.69±3.45	17.05±2.62	0.141	19.35 (17.7–22.3)	16.55 (13.82–17.75)	0.005*	75.18±7.8	69.57±9.46	0.014*

Mouth width (ch-ch), lower lip height (sto-is), and upper lip height (sn-sto)

Table 7. Comparison of the measurements of the ear region between the patient group and the control group

	Male			Female			All groups		
Measurement (mm)	Patient	Control	p	Patient	Control	p	Patient	Control	p
pra-pa (right)	37.6 (36.2–39.9)	40.1 (36.9–64.15)	0.095	36.05 (35.2–38.07)	38.85 (34.52–57.17)	0.331	37.2 (35.6–38.6)	40.1 (35.45–58.02)	0.025
pra-pa (left)	37.5 (36.6–38.9)	39.8 (37.1–64.3)	0.069	36.25 (34.9–38.3)	38.95 (34.45–57.2)	0.482	37.3 (35.6–38.8)	39.8 (35.4–57.85)	0.029
sa-sba (right)	64.0 (59.8–69.6)	65.85 (37.87–70.82)	0.893	64.15 (59.9–65.5)	62 (32.8–64.6)	0.083	64.0 (59.8–67.3)	62.8 (35.25–64.4)	0.276
sa-sba (left)	64.3 (60.2–68.2)	66 (38.15–60.85)	0.907	63.9 (60.05–65.5)	61.7 (32.02–64.65)	0.084	64.2 (60.1–67.2)	62.35 (35.17–68.42)	0.290

Ear width (pra-pa) and ear length (sa-sba)

of the controls ($p<0.05$). Ear lengths were not significantly different between the patients and controls ($p>0.05$, Table 7).

Discussion

Beta-thalassemia is distributed worldwide, particularly in Mediterranean countries. The Ministry of Health and National Hemoglobinopathy Council reported a 4.3% prevalence of the beta-thalassemia trait in 16 cities of the Turkish Mediterranean and Aegean region, which is more than twice the national thalassemia frequency [9]. Uysal et al. (15) reported that the prevalence of the beta-thalassemia trait in Izmir, which is the neighboring city of Aydin, was the highest in the Aegean region of Turkey (4.96%). Therefore, premarital screening or other necessary precautions should be strictly followed to - the increased prevalence of beta-thalassemia in this region.

During our study, measurements were taken from six craniofacial regions of the thalassemia major patient group and the control group. A total of 23 measurements were taken (2, 5, 4, 3, 5, and 4 for the cranial, bilateral ophthalmic, nasal, oral, facial, and bilateral aural regions, respectively). The results of the measurements increased our understanding of the craniofacial anatomy of thalassemia major patients and enabled us to obtain quantitative results. Similarly craniafacial measurements were performed by Farkas et al. [16] on Down syndrome patients. The authors identified measurements above and below the normal levels using 23 linear and 2 angular measurements taken from six craniofacial regions of 127 Down syndrome patients [16].

Our literature review did not yield any study that craniofacial anthropometric measurements in thalassemia patients. According to a review of craniofacial cephalometric studies conducted on thalassemia patients, it was found that Takriti et al. [17] had compared the skeletal and dental craniofacial parameters of 51 thalassemia major patients in Syria, obtained via lateral cephalometric radiograms, with the parameters of healthy subjects in the same age group. Class II malocclusion (where the upper teeth are more protruded than the lower teeth), maxillary prognathia and mandibular retrograph, rear face height reduction, and an increase in front facial height were identified [17].

In Qatar, Abu Alhaija et al. [5] conducted measurements of the lateral cephalograms of 37 thalassemia patients (24 males and 13 females between 5 and 16 years of age). The thalassemia group patients were found to have a class II skeletal model, and their maxillae were found to be normal in size; meanwhile, the smaller length of the cranial base was suggested to result from the short mandible [5].

Although our measurement methods were different, our measurements yielded a signifi-

cantly large nose width (al-al), upper lip height (sn-sto), and nasal root width (mf-mf) in the patient group; these findings are similar to the study by Takriti et al. [17]. In addition, among the facial measurements, face height (n-gn), nose height (n-sn), nasal tip protrusion (sn-prn), right and left ear width, mouth width (ch-ch), upper face height (n-sto), and lower face depth (t-gn) were significantly smaller. Nasal, aural, and oral measurements were shown in detail.

Abu Alhaija et al. [5] suggested that the severity of craniofacial deformities (CFDs) in β-thalassemia major patients would increase depending on age and the duration of symptoms. In a study conducted in Malaysia, Toman et al. [6] studied the frequency of CFDs and their relationship with the clinical picture. In total, 19 of 43 patients were found to have a CFD (44.2%; safety range, 30.2% to 58.2%), while no significant difference was found in the comparison between the CFD+ and CFD− groups in terms of clinical parameters [6].

In a study conducted in India, Girinath et al. [18] showed that oral and maxillofacial changes such as protrusion of the upper and lower jaws, saddle-shaped nose, gaps and protrusion in the frontal teeth, and frontal bulges were observed in 84% of the patients. They emphasized that the severity of the orofacial changes would increase with declines in both the health and blood charts of the patients. Moreover, they suggested that the prevalence of oral and maxillofacial changes would decrease in patients who underwent blood transfusions at a young age [18].

The subjects enrolled in our study were those who received regular treatment and controls. Therefore, the deformities observed in our subjects were not severe. The ability to demonstrate certain differences during the visual examination of the head and face were rather limited in previously conducted studies. These studies focused on a single craniofacial complex or only evaluated the morphological changes of certain craniofacial deformities [5, 17, 18]. Our study generated an extensive picture of all craniofacial complexes, and detailed data for visual examination were provided. The quantitative data obtained from the cranial and facial regions will assist in determining the defective elements to be surgically corrected in patients scheduled to undergo an operation.

Ethics Committee Approval: The study protocol was approved by the Human Ethics Committee of Adnan Menderes University and from Ministry of Health, Turkey.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors thank the doctors of Pediatrics and Hematology Clinics of State Hospitals at Aydin, Turkey for their contributions.

Author Contributions: Concept - S.K., Design - M.D.B.; Supervision - S.K.; Funding - A.M.T., S.O.C.; Materials - A.M.T., S.O.C., S.C.; Data Collection and/or Processing - A.M.T.; Analysis and/or Interpretation - I.K.O.; Literature Review - M.D.B.; Writing - A.M.T.; Critical Review - S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by a grant from Adnan Menderes University, Aydin, Turkey (through grant no. TPF- 10039).

References

1. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010; 12: 61-76. [CrossRef]
2. Oliver NF. The Beta-thalassemias. N Engl J Med 1999; 341: 99-109. [CrossRef]
3. Galanello R, Origa R. Beta-thalassemia. OJRD 2010; 5: 11-26. [CrossRef]
4. Bassimitci S, Yücel Eroglu E, Akalar M. Effects of thalassemia major on components of the craniofacial complex [Abstract]. Br J Orthod 1996; 23: 157-162. [CrossRef]
5. Abu Alhaija ESJ, Hattab FN, Al Omari MAO. Cephalometric measurements and facial deformites in subjects with β-thalessaemia major. Eur J Orthod 2002; 24: 9-19. [CrossRef]
6. Toman HA, Nasir A, Hassan R, Hassan R. Skeletal, dentoalveolar, and soft tissue cephalometric measurements of Malay transfusion-dependent thalassaemia patients. Eur J Orthod 2011; 33: 700-4. [CrossRef]
7. Aydinok Y. Thalassemia. Hematology 2012; 17: 28-31. [CrossRef]
8. Fettah A, Bayram C, Yarali N, et al. Beta-globin Gene Mutations in Turkish Children with Beta-Thalassemia: Results from a Single Center Study. Mediterr J Hematol Infect Dis 2013; 5: Open journal system. [CrossRef]
9. Canatan D, Kos MR, Ustundag M, Haznedaroglu D, Ozbas S. Hemoglobinopathy control program in Turkey. Community Genet 2006; 9: 124-6. [CrossRef]
10. Karakas S, Discigil G, Bilgin MD, Tekin N, Ozlem S. Evaluatıon of anthropometrıc measurements of a group of elderly from Turkey. Turk Geriatri Derg 2012; 15: 403-8.
11. Farkas LG, Deutsch CK. Anthropometric determination of craniofacial morphology. Am J Med Genet 1996; 65: 1-4. [CrossRef]
12. Farkas LG, Hreczko TM, Katic MJ, Forrest CR. Proportion indices in the craniofacial regions of 284 healthy North American white children between 1 and 5 years of age. J Craniofac Surg 2003; 14: 13-28. [CrossRef]
13. Kolar JC, Salter EM. Craniofacial Anthropometry. Practical Measurement of the Head and Face for Clinical, Surgical, and Research Use. Springfield, IL: Charles C Thomas Publisher; 1997.
14. Farkas LG. Anthropometry of the Head and Face. 2th ed. New York, NY: Raven Press, 1994.
15. Uysal A, Genc A, Tasyurek N, Turkyılmaz B. Prevalence of b-Thalassemia Trait and abnormal hemoglobin in premarital screening in the province of Izmir, Turkey. Pediatr Hematol Oncol 2013; 30: 46-50. [CrossRef]
16. Farkas LG, Katic MJ, Forrest CR, Litsas L. Surface Anatomy of the Face in Down's Syndrome: Linear and Angular Measurements in the Craniofacial Regions. J Craniofac Surg 2001; 12: 373-9. [CrossRef]
17. Takriti M, Dashash M. Craniofacial parameters of Syrian children B-thalassemia major. J Investig Clin Dent 2011; 2: 135-43. [CrossRef]
18. Girinath P, Vahanwala SP, Krishnamurthy V, Pagare SS. Evaluation of Orofacial Manifestations in 50 Thalassemic Patients: A Clinical Study. J of Indian Academy of Oral Med and Radio 2010; 22: 126-32. [CrossRef]