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Evaluation of the maxillomandibular positioning in subjects with sickle-cell disease through 2- and 3-dimensional cephalometric analyses

A retrospective study

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Abstract

Sickle-cell disease (SCD), which involves morphological changes to the red blood cells, is the most common hemoglobinopathy worldwide. This conformational change in erythrocytes affects multiple organs and systems, including the hard and soft tissues of the stomatognathic system. The objective of this study was to provide a description of the maxillomandibular positioning of patients using computed tomography in a case series of 40 patients with SCD. To define the facial profile of patients, 2-dimensional (2D) and 3-dimensional (3D) McNamara and Steiner cephalometric tracings were performed. The results showed that there is a tendency to maxillary protrusion in 2D and 3D analyses. There was no statistical difference between the 2D and 3D evaluations; additionally, sex affected the maxillomandibular positioning of patients, but only in McNamara evaluations.

Abbreviations: 2D = 2-dimensional, 3D = 3-dimensional, A-Nperp = McNamara maxillary positioning variable, CT = computed tomography, HbS = hemoglobin S, HUPES Complex = Professor Edgard Santos University Hospital Complex, Pog-Nperp = McNamara mandibular positioning variable, SCD = sickle-cell disease, SNA = Steiner maxillary positioning variable, SNB = Steiner mandibular positioning variable.

Keywords: cephalometric analysis, computed tomography, sickle-cell anemia, sickle-cell disease

1. Introduction

Sickle-cell disease (SCD) describes a group of autosomal recessive hemoglobin disorders.[1] It is the most common genetic disease of hemoglobin in the world and occurs when there is a missense mutation that results in the substitution of adenine to thymine at the 6th position of the hemoglobin beta gene.[2] This results in a glutamic acid to valine amino acid substitution, causing an altered phenotype with abnormal hemoglobin S (HbS), as opposed to hemoglobin A1, which is present in normal red blood cells.[3–5] A person homozygous for the HbS allele has a more severe presentation of sickle-cell anemia symptoms. If only 1 recessive allele (heterozygosis) is inherited, then the individual is only a carrier of the sickle-cell trait.[1,5–7]

Under hypoxic conditions, HbS polymerizes and causes the sickling of red blood cells. This morphological change is reversible through the supply of elevated oxygen levels. The constitutive changes in cell morphology results in cell membrane lesions that causes the cells to become rigid, preventing them from returning to their normal, physiological state.[5,8,9] This shortens the average life span of the red blood cells, and predisposes the individual to incidents of vaso-occlusion and hemolysis, pain episodes, and organ damage.[5,8–10]

Other manifestations of the disease include ulcers in the lower limbs, splenic sequestration, priapism, acute chest syndrome, aseptic necrosis of the femoral head, retinopathy, chronic renal failure, stroke, and the chronic involvement of multiple organs, systems, or devices.[6,11–13,15]

In Brazil, the diagnosis and genotyping of SCD is determined through a newborn screening test ("heel prick test"), in which blood is taken from the neonate's heel to allow for the electrophoresis or chromatographic evaluation of hemoglobin.[5,7]

Currently, SCD is prevalent throughout Europe and in some regions of Asia. In Brazil, especially in the State of Bahia, this hemoglobinopathy is quite prevalent and considered a public health problem. It is estimated that in Brazil, approximately 3500 children are born with SCD each year, and that 200,000 patients carry the mutation.[7] In the state of Bahia, there is an endemic focus of SCD, where a frequency of carriers of the sickle-cell trait was estimated in 5.5% of the general population, reaching 6.3% among those of African descent.[14]

In the bucomaxilofacial region, numerous changes are reported, such as the pallor of the oral mucosa, yellowing of the tissues, delayed dental eruption, hypomaturation and hypomineralization of enamel and dentin, hypercementosis, depapillation of the tongue, caries, pulp necrosis, periodontal

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Table 1

Variation in the McNamara parameters for the classification of the horizontal position of the maxilla and mandible.

	Retrusion	Normal	Protusion
Maxilla	A-Nperp ≤ -0.5 mm	-0.5 mm $\leq$ A-Nperp $\leq$ 2.5 mm	A-Nperp $>$ 2.5 mm
Mandible	Pog-Nperp ≤ -2 mm	+2 mm $\geq$ Pog-Nperp > -2 mm	Pog-Nperp $> +2$ mm
	Male sex	Male sex	Male sex
	Pog-Nperp ≤ -4 mm	0 mm $\geq$ Pog-Nperp > -4 mm	Pog-Nperp $>$ 0 mm
	Female sex	Female sex	Female sex

A-Nperp = maxillary positioning values, Pog-Nperp = mandibular positioning values.

disease, radiographic alterations, craniofacial bones abnormalities, and the incidence of malocclusions.[5,13,16]

Although many authors describe the high frequency of malocclusions, facial profile changes and abnormalities in the size and shape of maxillary bones in people with SCD, the direct relationship between oral/craniofacial manifestations and SCD is not completely established. Costa et al,[17] for example, believed that there was no significant evidence to confirm SCD as a risk factor for craniofacial changes and malocclusion.

Thus, the objective of this study was to evaluate and describe the cephalometric pattern in a case series of 40 individuals diagnosed with SCD. In addition, the 2-dimensional (2D) and 3-dimensional (3D) techniques were compared to each other, and the relationship between maxillomandibular positioning and sex was evaluated.

2. Materials and methods

This study was approved by the Research Ethics Community of the Professor Edgard Santos University Hospital Complex (HUPES Complex) of the Federal University of Bahia (CAAE: 18689114.8.0000.0049, opinion number 993.255 of 2015).

The members of this study had previous diagnosis of SCD through the newborn screening test, or electrophoresis or chromatographic evaluation of hemoglobin. These people were referred to the HUPES Complex Dental Care Service by the Municipal Outpatient Clinic of SCD or by the Hematology or Orthopedics Services of the HUPES Complex from February 2015 to December 2016.

Forty individuals diagnosed with SCD, who consented and completed the Informed Consent Form, were included in this study. Those considered for the study had to be over 19 years of age, have no other systemic diseases affecting bone metabolism, and were required to undergo an imaging assessment of the face.

The participants were examined in dental office of the HUPES Complex by a dental surgeon. Biosocial information was collected, such as the age and sex. Information regarding genotype of the disease was collected from the medical referral report. Following a clinical and imaging examination, a dental diagnosis was established. The patients underwent adjustment of the oral environment and, considering their systemic condition, were referred for specialized treatments if necessary.

When an imaging evaluation of the face was indicated, the patients underwent a computed tomography (CT) scan of the face with a cone beam or multislice equipment, where fine axial volumetric cuts were obtained within a bony window, without intravenous organo-iodized contrast injection. The images were exported in a Digital Imaging and Communication in Medicine format to an electronic media and archived. The CT scans were processed in Dolphin software to obtain 2D and 3D virtual reconstructions of the face. The steps for generating the reconstructions were standardized. The reconstructed images were saved for later analysis for a single examiner, who was a specialist in orthodontics.

Three-dimensional reconstructions of face CT scans were performed using the McNamara and Steiner tracings, which were adapted for 3D images. These tracings were chosen to evaluate the maxillomandibular positioning of the face in a linear and angular way. The values indicating the positioning of the maxilla and the mandible, in relation to the skull base, for the 2 analyses were used. McNamara analysis was based on the evaluation of the maxillary (A-Nperp) and mandibular (Pog-Nperp) positioning values, according to the following criteria (Table 1).

Steiner analysis was based on the evaluation of the maxillary (SNA) and mandibular (SNB) positioning values, according to the following criteria (Table 2).

The values used as a reference were obtained based on the studies of Ellis and McNamara,[18] McNamara,[19] and Steiner.[20]

Following evaluation, 3 possible diagnoses were established for the maxilla and/or mandible: protruded, retruded, or neutral.

The biosocial data were submitted for descriptive analysis, including the results of the cephalometric patterns. The distribution of the studied variables was tested by the Kolmogorov–Smirnov test. After checking for normality, the comparison of cephalometric measurements in 2 and 3 dimensions was performed by applying the Student *t* test. The level of significance adopted was 5%. The statistical program SPSS version 17.0 was used to perform the analysis.

3. Results

3.1. Biosocial data

The first 40 individuals with a confirmed diagnosis of SCD, aged between 20 and 60 years old, were included in this case series. The patients were evenly distributed in terms of sex (20 male patients and 20 female patients), and had an average age of 35 years.

Only 2 patients did not respond to the "skin color" variable in the questionnaire. The remainder of the patients provided either of the following written responses: "black" (n = 18/45.0%) or "brown" (n = 20/50.0%). In addition, the majority of (n = 16/40.0%) patients had a diagnosis of homozygous genotype for sickle cell disease type of SCD; however, many medical referral

Table 2

Variation of Steiner parameters for the classification of the horizontal positioning of the maxilla and mandible.

	Retrusion	Normal	Protusion
Maxilla	SNA $\leq 80.5°$	$80.5° >$ SNA $\geq 83.5°$	SNA $> 83.5°$
Mandible	SNB $\leq 78.5°$	$78.5° >$ SNB $\geq 81.5°$	SNB $> 81.5°$

SNA = maxillary positioning values, SNB = mandibular positioning values.

Table 3

Sample distribution according to sex or racial profile.

Variables	n (%)
Sex	
Male	20 (50.0)
Female	20 (50.0)
Skin color	
Black	18 (45.0)
Brown color	20 (50.0)
Not informed	2 (5.0)
Genotype	
HbSS	16 (40.0)
HbSC	11 (27.5)
Others	1 (2.5)
Not informed	12 (30.0)

HbSC = heterozygous genotype for sickle cell disease, HbSS = homozygous genotype for sickle cell disease.

reports did not provide information of genotype, so there was no information of genetic profile of disease in 30.0% (n = 12) of participants, as shown in Table 3.

3.2. Two- and three-dimensional evaluations

McNamara and Steiner cephalometric variables were evaluated using 2D and 3D techniques, and no statistically significant differences were evident between the 2 methods (Table 4).

This means that those methods are equally effective in determining horizontal positioning of the maxilla and mandible; that is, although there are different evaluation methods, there are no different diagnoses of protrusion, retrusion, or neutrality of maxillary bones.

3.3. Facial profile of individuals with SCD

The evaluation of the facial profile of patients with SCD showed A-Nperp and SNA variables with a tendency to protrusion across all analyses. The results of 2D evaluation can be observed in Table 5, while the results related to 3D evaluation are represented in Table 6.

For mandibular positioning, the incidence of retrusion was evident, but only for SNB 2D and SNB 3D variables (Tables 5 and 6).

3.4. Facial profile and sex

Regarding the association between sex and the maxillomandibular positioning parameters, it was observed that the Pog-Nperp variable presented statistical significance for both 2D and 3D techniques ($P = .05$) (Table 7). Men had mean values for Pog-Nperp variable of −4.92 mm, while women had mean values of 0.22 mm in 2D technique. In 3D technique, men presented mean values of −2.93 mm and women 1.56 mm (Table 3).

Therefore, men present mandibular retrusion, while females present mandibular protrusion, in this population, in 2D and 3D evaluations.

Table 4

Comparison of Steiner and McNamara cephalometric measures in 2D and 3D.

	2D	3D	*P*
A-Nperp	4.11 mm	4.81 mm	.41
Pog-Nperp	2.35 mm	6.69 mm	.34
SNA	83.40°	83.56°	.87
SNB	78.19°	77.44°	.54

A-Nperp = maxillary positioning values, Pog-Nperp = mandibular positioning values, SNA = maxillary positioning values, SNB = mandibular positioning values.
$P < .05$ indicates a statistically significant difference.

Table 5

Distribution of the cephalometric pattern according to McNamara and Steiner 2D analyses.

	A-Nperp (2D), n (%)	Pog-Nperp (2D), n (%)	SNA (2D), n (%)	SNB (2D), n (%)
Retrusion	5 (12.5)	17 (42.5)	9 (22.5)	**21 (52.5)**
Average value	−1.72 mm	−9.89 mm	77.97°	74.82°
Neutrality	10 (25)	10 (25.0)	10 (25.0)	13 (32.5)
Average value	1.11 mm	−1.26 mm	82.22°	80.07°
Protusion	**25 (62.5)**	13 (32.5)	**21 (52.5)**	6 (15.0)
Average value	6.48 mm	6.67 mm	86.29°	85.83°

Bold-emphasized numbers represent the highest frequency of cases.
A-Nperp = maxillary positioning values, Pog-Nperp = mandibular positioning values, SNA = maxillary positioning values, SNB = mandibular positioning values.

4. Discussion

The 3D evaluation of the maxillomandibular positioning of patients with SCD allowed us to observe that, in this population, there was a slight prevalence of maxillary protrusion associated with mandibular retrusion. Considering that the present population mostly sampled individuals of African descent, the results of the present study contradict previous cephalometric studies of the black population, which often indicate a prevalence of biprotrusion in the affected demographic.[21,22] Maxillary protrusion associated with mandibular retrusion provides evidence for the mechanism of compensatory medullary hyperplasia in SCD as growth and advancement were observed only in the maxilla.

Compensatory growth occurs only in the spongy maxillary bone, which has a wider medullary cavity and thinner cortical spaces. This allows for greater oxygenation to the region.[23] In patients with SCD, medullary hyperplasia is compensatory due to chronic and prolonged anemia, which increases the hematopoietic demand. Over time, this causes the residual red bone marrow to react hyperplastically, resulting in cortical expansion and bone deformity. SCD is manifested by a greater oxygen demand in the region of the maxillary bone, in order to avoid hypoxia and tissue failure in situations of low oxygenation.[17,24]

The high sampling frequency of black individuals in this case series is justified by the historic prevalence and distribution of

Table 6

Distribution of cephalometric patterns according to McNamara and Steiner analyses in 3D.

	A-Nperp (3D), n (%)	Pog-Nperp (3D), n (%)	SNA (3D), n (%)	SNB (3D), n (%)
Retrusion	3 (7.5)	13 (32.5)	13 (32.5)	**23 (57.5)**
Average value	−1.56 mm	−8.60 mm	78.5°	74.19°
Neutrality	6 (15.0)	13 (32.5)	5 (12.5)	11 (27.5)
Average value	0.70 mm	−0.68 mm	83.04°	79.93°
Protusion	**31 (77.5)**	14 (35.0)	**22 (55.0)**	6 (15.0)
Average value	6.23 mm	6.67 mm	86.65°	85.28°

Bold-emphasized numbers represent the highest frequency of cases.

Table 7

Comparison of the means of Steiner and McNamara cephalometric measures, in relation to the sex of the participant.

	Female	Male	*P*
A-Nperp 2D	5.12 mm	3.11 mm	.11
A-Nperp 3D	5.71 mm	3.92 mm	.12
Pog-Nperp 2D	.22 mm	−4.92 mm	**.05**
Pog-Nperp 3D	1.56 mm	−2.93 mm	**.05**
SNA 2D	83.72°	83.08°	.62
SNA 3D	84.34°	82.77°	.27
SNB 2D	78.8°	77.57°	.40
SNB 3D	78.65°	76.21°	.21

Bold-emphasized numbers represent statistically significant data, where statistical significance was defined as $P < .05$.

A-Nperp = maxillary positioning values, Pog-Nperp = mandibular positioning values, SNA = maxillary positioning values, SNB = mandibular positioning values.

SCD among individuals of African descent. Although the geographic distribution and epidemiology of SCD can be traced back to Asia Minor, the massive slave trading that occurred between the fifteenth and nineteenth centuries allowed for the spread of the disease worldwide, especially throughout the Americas. Currently, although SCD is distributed homogeneously worldwide, this hemoglobinopathy has a higher prevalence among populations wherein the declared proportion of African descent is higher, such as in Bahia.[13,25,26]. According to the Brazilian Demographic Census,[27] Bahia is a state with the highest census of black individuals, totaling 76.3% of the population, with only 22.2% of the population consisting of Caucasian individuals.

Although a more convex facial profile with maxillary advancement and mandibular retrusion has been described in this population, this study did not present a control group to compare the results found, which represents limitations regarding cephalometric normalization of SCD people. The literature states that cephalometric standardization should be relativized according to age, sex, facial type, anatomical limitations, and ethnic differences, so that the normality patterns of each population are respected.[20] On the other hand, although few studies have evaluated the specificities of the Brazilian facial profile (with or without SCD) using McNamara or Steiner methods, the criteria proposed by these works are robust enough to be used as a comparison parameter in the Brazilian population, and, consequently, in the present study.

Nevertheless, the scarcity of studies evaluating the facial skeletal pattern of specific populations, such as this one, reinforces the need to develop further studies that determine not only the anteroposterior position of the maxilla and mandible in relation to the base of the skull, but also the transverse width of these maxillary bones and the impact caused in the occlusion, respiration, and esthetics.

Radiographic cephalometry has been documented since 1922, when Pacini[28] described the relationship between gnathic teeth and bones, in relation to the base of the skull, within a geometric scheme. This method became viable and universal after the standardization of Broadbent cephalometric radiographs[29] in 1931, with the use of a cephalostat apparatus. Since then, many cephalometric analyses have been developed, allowing for studies on craniofacial development and growth, studies on malocclusions, and increased public discourse between professionals, patients, and relatives on the related topics.

Currently, many researchers have been conducting studies in an attempt to demonstrate the applicability of cephalometric analysis in 3D images; however, there is still controversy in the literature regarding the use of this method. Some obstacles were encountered during the analysis; for example, conventional cephalometric parameters were largely inapplicable to 3D images as they use flat and nonvolumetric quantities. In addition, facial asymmetries are easily observed during 3D examinations, which make it difficult to perform cephalometric evaluations.[30,31]

However, in this case series, no statistically significant differences regarding 2D and 3D cephalometric evaluations were evident, which is an aspect of great relevance for the diagnoses of maxillomandibular positioning. Since the 3D cephalometric evaluation method is incapable of affecting the final diagnostic outcome of the facial profile, it can be considered a reliable and safe method for analysis. In addition, these results highlight the feasibility of transposing McNamara and Steiner 2D parameters to volumetric evaluations through tomographic cuts, without altering the diagnosis of the patient. Therefore, the use of cephalometric measurements during 3D sequencing may play a vital role for the therapeutic planning of orthodontic, surgical, or orthosurgical outcomes.

Additionally, the apparent sexual dimorphism between patients reinforces the application of McNamara parameter in 3D cephalometric analyses. In the study of Ellis and McNamara[18] and McNamara,[19] in establishing the positional patterns of the mandible relative to the base of the skull, the authors delineated between the values for the male and female sexes. The differences in linear anthropometric ratios between male and female patients have repercussions for conventional cephalometric standards. These differences were further demonstrated in the present study, where the Pog-Nperp variable in the 3D images, which determines mandibular positioning in relation to the base of the skull, presented a statistical difference between the sexes ($P = .05$). Thus, the use of 3D cephalometric analysis in the present study was consistent with the statistical normalization modeled by Ellis and McNamara[18] and McNamara[19] and reinforces the reliability of 3D evaluations when compared to conventional evaluations.

5. Conclusions

The use of CT for the evaluation of the maxillomandibular positioning of patients with SCD demonstrated that there were no statistical differences between the 2D and 3D evaluations. In addition, it showed that there was a predominance of maxillary advancement, in relation to the base of the skull, in both McNamara and Steiner evaluations for 2D and 3D images.

Following Steiner evaluations of the 2D and 3D images, the results were consistent with those associated with a retruded mandible, in relation to the base of the skull. Therefore, in the present study, according to Steiner analysis, there was a higher frequency of facial profiles with a protruding maxilla and a retruding mandible in individuals with SCD.

The relationship between sex and mandibular positioning was significant in 2D and 3D images, but only with McNamara analysis.

Although it is a series of cases, through this study it was possible to ratify the possibility of transposition of 2D cephalometric parameters for 3D evaluations. In addition, it is expected that the knowledge of the facial skeletal profile of people with DF supports specific therapeutic actions for this population.

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