Gnathopathy In Sickle Cell Disease: Anthropometric And Cephalometric Assessment Of Ghanaian Patients

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Abstract

Introduction: One of the dentofacial complications of Sickle Cell Disease (SCD) is an increased incidence of protrusion of the maxilla in SCD patients known as Sickle Cell Gnathopathy. The increased protrusion of the maxilla is hypothesized to be the result of bone marrow hyperplasia that is present in several individuals with Sickle Cell Anemia (SCA). This study aimed to determine the morphological characteristics of gnathopathy in SCD patients in Ghana.

Methods: This was a cross-sectional study involving 94 participants with Sickle Cell disease (46 males, 48 females). Sixty-five (69.14%) of them having Haemoglobin SS genotype, and 29 (30.85%) having haemoglobin HbSC genoptype. Anthropometric data comprising the height and weight of participants was collected and the Body Mass Index calculated. The hemoglobin levels for each participant were also measured. Lateral cephalometric radiographs were taken using a Carestream CS8100 cephalostat. The digital radiographic images were traced and analyzed with Audax Ceph Advantage Software version 5.2.0.3610. Statistical analysis was performed with SPSS version 23 software using correlation t-test and logistic regression. A statistical significance was set at a p-value of <0.05 at a 95% Confidence Interval.

Results: The mean age ± standard deviation of participants was 28±9.3 years. The mean BMI of participants was 21.95±4.53kg/m^2. There was a statistically significant difference between the BMI of HbSS individuals 20.35±2.83kg/m^2 and HbSC individuals 23.44±5.30kg/m^2 (p-value=0.00). With respect to genotype, HbSS individuals had an increased by 8.4% in (MMPA):30.08±4.97o when compared to HbSC individuals 27.76±5.08o (p=0.03). An assessment of the prevalence of maxillary protrusion showed that 18.1% of SCD patients had maxillary protrusion and 8.5% of SCD patients had excessively proclined maxillary incisors.

Conclusion: This study provides preliminary cephalometric data on the basic craniofacial characteristics of SCD patients in Ghana. Female SCD patients had a greater MMPA and reduced palatal length when compared with male counterparts. HbSS individuals had a greater MMPA angle when compared with HbSC individuals.

Keywords: Gnathopathy, cephalometric data, craniofacial characteristics, Sickle cell disease.

Introduction

Sickle cell disease (SCD) is a major global public health concern of which sub-Saharan Africa bears the greatest burden.[1] SCD is an umbrella term for all mutations in the β-globin gene that precipitate the same clinical syndrome.[2] Sickle cell anemia (SCA) is the most common form of SCD and results from the homozygous inheritance of the βS-mutation. It is responsible for about 70% of all SCD cases globally.[3] SCD can also result from the heterozygous inheritance of the HbS in combination with other mutations resulting in conditions such as but not limited to Haemoglobin SC disease, HbS, and β-thalassemia.[4]

The persistence of SCD in the sub-Saharan African population appears to be greater than the rest of the world because the carriers of the sickle mutation are protected from severe malaria.[5,6] Unfortunately, homozygotes develop SCA and suffer several complications of the disease. Indeed, without treatment, several children with SCA die before they turn 5 years old.[7] In Ghana, 2% of all newborns have SCD and more than half of these (55%) have the homozygous form (SC).[8]

The primary cause of SCD, Hemoglobin S (HbS) is a point mutation in the gene for β-globin where the adenine is substituted for thymine at the 17th nucleotide. This results in the change from glutamic acid to valine at the sixth amino acid in the β-globin chain.[9] This results in the creation of a hydrophobic motif in the HbS tetramer when deoxygenated and subsequently results in the binding of the β1 and β2 chains of two hemoglobin molecules. A polymer nucleus is thus created, grows, and eventually fills the red blood cell. This results in a disruption of the architecture of the erythrocyte and affects its flexibility.[10]

SCD frequently exhibits several multi-systemic manifestations such as acute chest syndrome, pulmonary hypertension, leg ulcers, gallstones, priapism, etc. Bone involvement in SCD also occurs and complications such as osteomyelitis, bone marrow necrosis and bone infarcts are relatively common.[11] The craniofacial skeleton is not spared in SCD and complications such as turricephaly (tower skull), frontal and parietal bossing, altered trabecular bone patterns and gnathopathy have been shown to occur.[12]

The association of gnathopathy with SCD has however not been conclusively established. Several studies on the subject have proffered conflicting results. Brown and Sebes, Mourshed and Tuckson and Shnorhakian et al have all reported an increased incidence of maxillary protrusion amongst individuals with SCD.[13,14] Fernandez et al and Maia et al reported that it appears the bones of the face are not often affected by marrow hyperplasia.[15,16] These conflicting findings, coupled with the fact that gnathopathy is not a constant finding in patients with SCD suggest that, possibly, like several other complications of SCD, the presence and severity of gnathopathy may be modulated by other factors which could be genetic or environmental.

Sickle cell gnathopathy is a major craniofacial complication of SCD and has significant effects on the quality of life of affected individuals. Studies exploring complications of SCD in Ghana as well as factors that possibly influence its presentation is lacking in the literature. A study of this nature is therefore warranted to provide more information on this interesting clinical phenomenon. This study aims to determine the morphological characteristics of gnathopathy in SCD patients in Ghana.

Methods

A cross-sectional study involving adults with SCD at the Sickle Cell Clinic of the Korle-Bu Teaching Hospital (KBTH) in Accra. Ethical approval was sought from The Ethical and Protocol Review Committee of the School of Biomedical and Allied Health Sciences (ID no. SBAHS – PHYSIOLOGY/10104854/SA/2019), University of Ghana, and the Korle-Bu Teaching Hospital (ID no. KBTH-STC 000125/2019). The study population consisted of adult laboratory diagnosed SCD patients reporting at the Sickle Cell clinic between the dates of 20th July 2020 and 14th August 2020. Participants included adult laboratory diagnosed SCD patients from the ages of 18-60years attending the Sickle Cell Clinic. Using a systematic sampling

technique, a sample frame was obtained from the Sickle Cell Clinic Registry. Six (6) patients were recruited per day. Using a sampling interval k = total clinic booking / 6, a total of 6 folders were chosen each weekday by selecting every kth folder that met the inclusion criteria. The 1st patient was chosen by simple balloting from the clinic registry and every k^{th} patient after him/her was recruited into the study until the sample size was obtained. This was done to avoid sampling bias and thus improve the generalizability of the data collected. A total sample size of 92 people was recruited for the study.

Adult SCD participants who consented to take part in the study were screened by interviewing them to obtain any relevant information that may not be in their medical records. Their medical history was also obtained from medical records/ folders. Using a well-structured questionnaire, information on demographics, frequency of crisis in the past 1-year, and last blood transfusion were obtained from participants. Information obtained was corroborated with patient's medical history where applicable. Instruments were calibrated to ensure reliability and accuracy.

Using an Omron® digital weighing scale and a standard meter rule, patients' weight and height were obtained. The scale was placed on a flat horizontal surface. Weight was measured with participants barefooted and wearing light clothing and was recorded to the nearest 0.1kg. Height was also measured using a meter rule with patients upright and shoulders in normal alignment. The height in centimeters was then converted to meters. Body mass index (BMI in kg/m^2) was calculated for each participant as the individual's body weight (in Kilograms) divided by the square of his/her height (in meters). The values were then recorded on a form.

A standardized radiographic technique was employed in acquiring the lateral cephalograms. The cephalograms were taken with a cephalostat (Carestream CS 9000) as shown in figure 1 with the head positioned parallel to the Frankfort plane (a plane used in craniometry that is determined by the highest point on the upper margin of the opening of each external auditory canal or external acoustic meatus and the lowest point on the lower margin of the left orbit and that is used to orient a human skull or head usually so that the plane is horizontal), with teeth in habitual occlusion and the lips relaxed (Figure 2). The digital images obtained were traced and analyzed using Audax Ceph Advantage Software version 5.2.0.3610.

Figure 1 A picture of the Cephalostat (Carestream CS 9000) used in this study

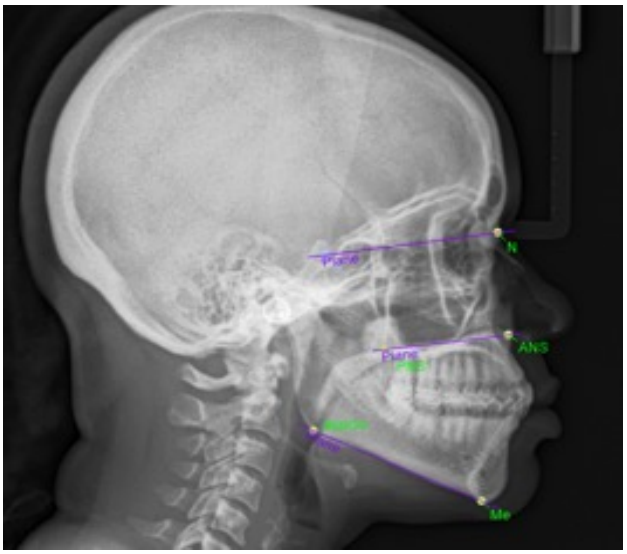

Figure 2 Facial dimensions

Data was stored anonymously with each patient having a unique identifier. To maintain confidentiality, the principal investigators kept records in locked cabinets and results of tests were coded to prevent association with patient names. Data collected was entered into and analyzed with SPSS version 25 software. All values were expressed as mean (M) ± standard deviation (SD). The

differences between two means were analyzed using the Student t-test for unpaired data. All p-values less or equal to 5% were judged statistically significant. Risk analysis was used to establish association between independent variables and outcome.

Results

Demographic and Anthropometric data of participants

This study involved 94 participants with SCD HbSS and HbSC genotypes, comprising 46 males and 48 females. The mean age of the participants was 28±9.3 years.The ages of participants ranges from 18-54 years. Most participant were diagnosed after 5 years of age (Table 1).

Table 1 Age of first diagnosis

Age	Frequency	Percentage
0-1years	12	12.8
>1-5years	32	34.0
>5-12years	29	30.9
>12-19years	16	17.0
>19years	5	5.3

The SCD patients were made up of 69.1 % homozygous SS, 30.9% heterozygous SC genotype. With respect to the educational level of participants, majority of the individuals 79(84.1%) either had 40(42.6%) high school or 39(41.5%) tertiary education, 14.9% with basic education and 1.1% with no formal schooling (Table 2). The mean height for all participants was 1.64±0.07 m, whilst the mean weight was 59.48±11.98 kg. The mean BMI was 21.95±4.53.

Table 2 Demographic data of participants (N=94)

Variable	Total n(%)	Gnathopathy n(%)	Normal n(%)	OR (95%(C.I)	p-value
Gender					
Male	46(100.0)	11(23.91)	35(76.09)	2.20(0.73-6.55)	0.15
Female	48(100.0)	6(12.50)	42(87.50)	1	
Education level					
No education	1(100.0)	0(0.0)	1(100.0)		
Basic School	14(100.0)	5(35.71)	9(64.29)	4.86(1.07-21.8)	0.03*
High School	40(100.0)	8(20.00)	32(80.00)	2.18(0.04-0.3.2)	0.23
Tertiary	39(100.0)	4(10.26)	35(89.74)	1	
Genotype					
SS	65(100.0)	12(18.46)	53(81.54)	1.08(0.34-3.42)	0.88
SC	29(100.0)	5(17.24)	24(52.76)	1	
Chronic illness					
Yes	9(100.0)	2(22.22)	7(77.78)	1.33(0.25-7.06)	0.73
No	85(100.0)	15(17.65)	70(82.35)	1	
HB					
Mild anemia	15(100.0)	3(18.75)	13(81.25)	0.83(0.16-3.40)	0.31
Moderate anemia	23(100.0)	5(21.74)	18(18.26)	0.84(0.16-4.11)	0,05
Normal	14(100.0)	3(21.43)	11(78.57)	1	
Severe anemia	15(100.0)	3(20.00)	12(80.00)	0.92(0.15-5.40)	0.07

Abbreviations: n (%), frequency and percentages; *, significance; SS, Hemoglobin SC; OR, odd ratio; CI, Confident Interval

For male respondents, the mean BMI was 20.72±3.62 whilst that for the female respondents was 24.64±5.30 kg/m². In terms of genotype, individuals with HbSS had a mean BMI of 20.35±2.83 whilst those with an HbSC genotype had a mean BMI of 23.44±5.30 kg/m², a difference that proved to be statistically significant (p=0.00). Majority (64) of participants had a normal BMI constituting 68.1% of participants, 10 (10.6%) individuals were classified as overweight, 7 (7.5%) individuals were classified as obese. 13.8% of individuals were however classified as underweight.

From the study, the prevalence of gnathopathy was 18% among people with SCD (Figure 3).

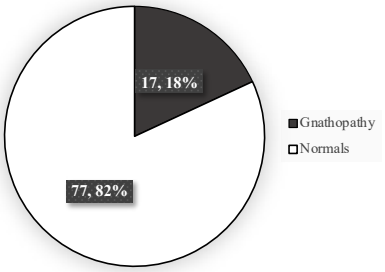

Figure 3 Prevalence of gnathopathy

Values for Hb levels were obtained for 68 participants of the study. The mean Hb level was 8.8±2.2g/dL. Male respondents had a mean Hb of 9.20±2.55g/dL whilst females had a mean Hb level of 8.34±1.96g/dL. In comparing the Hb values for individuals with the 2 different genotypes, a statistically significant difference was noticed as HbSS individuals had an average Hb of 7.64±1.65 g/dL whilst HbSC individuals had an average Hb of 11.07±1.58 g/dL(p-value=0.00).

Cephalometric analysis

An assessment of the anteroposterior dimensions of the face was done by measuring Sella-Nasion-A point angle (SNA), Sella-Nasion-B point angle (SNB) and A point-Nasion-B point angle (ANB) values. The mean SNA values for all participants were 88.37±4.6° (Figure 4). SNB values were 83.31±3.8° and average ANB values for all participants was 5.05±2.6°. The average palate length was 49.3±3.1mm (Table 3). To assess vertical facial dimensions, the maxillary-mandibular plane angle (MMPA) and the lower anterior facial height (LAFH) were assessed. Mean MMPA values for all participants was 29.36±5.0° whilst mean LAFH value was 58.41±2.3%.

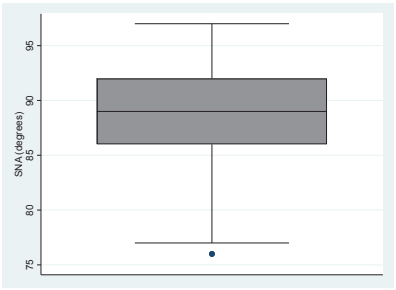

Figure 4 distribution of SNA

An assessment of incisor position relative to the respective dental bases was done by measuring both the upper incisor – maxillary plane (UIMxPl) angle and lower incisor mandibular plane (LIMnPl) angle. The mean UIMxPl angle was 117.48±47° and the mean LIMnPl angle was 103.3±6.59°. The mean interincisal angle was 110.0±9.9°. When compared with the norms for the Ghanaian population as proposed by Fadeju et al.[17] Statistically significant differences were noted in the MMPA, LAFH, UIMxPl and LIMnPl values (p-value=0.00).

Table 3 Dentofacial measurements and independent variables

Cephalometry	Mean (SD)	Weight	Age
SNA^{O}	88.37±4.6	0.12(0.24)	0.02(0.84)
SNB^{O}	83.31±3.8	0.20(0.04*)	-0.11(0.25)
ANB^{O}	5.05±2.6	-0.08(0.42)	0.20(0.05)
Length of palate (ANS-PNS)	49.3±3.1	0.08(0.43)	0.09(0.37)
MMPA^{O}	29.36±5.0	-0.04(0.69)	0.08(0.43)
LAFH (%)	58.41±2.3	0.24(0.01*)	0.12(0.26)
UIMxPl^{O}	117.48±7.3	0.07(0.458)	-0.08(0.43)
LIMnPl^{O}	103.30±6.6	0.12(0.22)	0.09(0.34)
IIA^{O}	110.00±9.9	-0.12(0.24)	-0.04(0.56)

Abbreviations: SNA, Sella Nasion A-point angle; SNB, Sella Nasion B-point angle; ANB, A-point Nasion B-point angle; MMPA, Maxillary Mandibular planes angle; LAFH, Lower Anterior Facial Height; UIMxPl, Upper Incisor Maxillary Planes angle; LIMnPl, Lower Incisor Mandibular Planes angle; IIA, Inter-incisal angle; **, Correlation and significance; SD, standard deviation.

Correlation of SNA and age has been shown in figure 5.

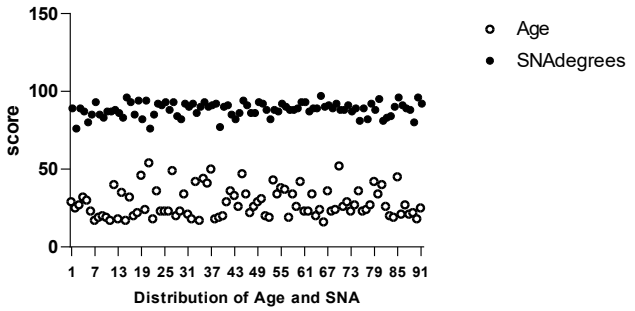

Figure 5 Distribution of SNA and age score (correlation coefficient of +0.02)

Assessment of gnathopathy, skeletal base relationship and incisor proclination

To assess maxillary prognathism, SNA values were compared to upper limit for the norms of the Ghanaian population (88.60±4.02°) proposed by Fadeju et al.[17] From the study, SCD individuals 17(18.1%) had increased SNA values suggestive of a prognathic maxilla. Of this number, 11% were males and 6% were females. Furthermore, 12 individuals with HbSS genotype and 5 individuals with HbSC genotype had an SNA value greater than the upper limit for norms of the Ghanaian population. ANB values were also assessed to determine the skeletal relationship between the maxilla and mandible. These values were compared to the upper limit of the norms for the Ghanaian population (5.37±2.24°). Results from the study show that, 21.3% of participants had increased ANB values. In assessing upper incisor protrusion, UIMxPl values were compared with the upper value for the norms of the Ghanaian population (120.94±7.13°). Some of the participants (8.5%) were determined as having excessively proclined maxillary incisors.

Discussion

This study sought to evaluate the craniofacial characteristics of individuals with Sickle Cell disease. A total of 94 participants were recruited in the study. This number comprised 46 males and 48 females. This shows a nearly equal distribution of gender among people living with SCD. Individuals with HbSS constituted most participants (69.1%) whilst those with HbSC constituted the minority (30.9%) and this shows that almost two-thirds of people living with SCD are HBSS. With respect to the level of education of participants, majority either had a secondary or tertiary education (84.1%) and this have contributed to lifestyle changes and management practices of SCD patients improving their quality of life. This could be explained by the fact that the study was carried out in an urban area which typically presents greater access to education than in rural settings.[18] This is an important finding considering the reported cognitive and academic impacts of the disease on affected individuals.[19] A descriptive study carried out by Nettles also concluded that individuals with SCD were at a greater risk of school failure than their healthy peers.[20] On the other hand, studies by Ezenwosu and Ogunfowora demonstrated no significant difference in the academic performance and achievement between individuals with SCD and healthy controls.[21]

Most participants in this study were classified as having normal weight with only 13.8% of participants classified as underweight. This relatively reduced proportion when compared to other studies could be due to the general improvement in care received by SCD patients.[22,23] It could also be because this study combined both individuals with Sickle Cell Anemia SCA (which is the more severe form of the disease) and HbSC individuals who in general have less severe disease experience. Indeed, several studies have shown a significant difference in the BMI of individuals with HbSS and HbSC a phenomenon that has also been demonstrated in this study.[24] In addition, our study revealed 18.1% of SCD patients as either being overweight or obese. This could be explained by the recent trend of obesity in the general population. Ballas et al, detailed the increase in body mass index of SCD patients particularly in females. [25]

This study revealed that only 12.8% of individuals were diagnosed between birth and 1-year-old. Many participants were diagnosed with the disease after 5 years of age. This clearly shows the large gap in diagnosis. Several countries, Ghana inclusive, have initiated neonatal screening procedures for SCD and it is possible that the individuals included

in this study precluded the generation that enjoyed this privilege.[26] The screening of newborns with sickle cell program is a prime example and continues to help educate and engage caregivers in how children are cared for.

Clinic attendance is an essential part of the management of individuals with SCD. Standard SCD practice guidelines recommend that patients ages 2 years and older attend routine clinic appointments every 6 months, and more frequently if needed.[27] In this study, the majority (91.5%) of participants reported regular clinic visits of 6 months or earlier.

The dentofacial characteristics of individuals with HbSS and HbSC were also assessed in this study. HbSS individuals in this study had a greater mean MMPA value when compared to HbSC individuals and this may suggest that HbSS patients may have a clockwise direction of growth when compared to their HbSC counterparts. In addition, although mean LAFH was greater in HbSS participants, the difference was not statistically significant. These two findings suggest that HbSS individuals are more likely to have a dolichofacial appearance with a clockwise rotation of the mandible when compared to HbSC individuals. Different cephalometric variables have been utilized in the assessment of gnathopathy amongst SCD individuals. In this study, the SNA variable was assessed as a measure of maxillary prognathism. When compared to Ghanaian norms, 18.1% of our sample had maxillary prognathism (gnathopathy). A study also reported that 34% of SCA patients had a protruded maxilla.[16] No study was found to have assessed the prevalence of maxillary prognathism in the general Ghanaian population and therefore it is difficult to make a statement on the increased prevalence of gnathopathy amongst SCD patients in Ghana. This is the first Ghanaian study assessing facial characteristics of SCD patients using cephalometric methods. A greater percentage of males in this study were found to have prognathic maxillae when compared to female SCD patients. Also, a greater percentage of HbSS patients had gnathopathy when compared with HbSC. An assessment of the ANB angle is also frequently undertaken in the assessment of gnathopathy amongst individuals with SCD.[16,28] This study showed that 21.3% of SCD patients had an increased ANB angle and therefore had more convex facial profiles. A greater percentage of females (25.0%) than males (17.39%) presented with this. A greater percentage of HbSS individuals (23.08%) also presented with a large ANB angle when compared with HbSC individuals (17.24%). Incisor protrusion is often a feature of maxillary protrusion, especially if severe. This increased proclination of the upper incisors is thought to be due to the difficulty in achieving an oral seal and therefore to positioning of the lower lip behind the upper incisors resulting in increasing proclination from the pressure of the lower lip.[29] The orthodontic management of such incisor proclination in SCD patients has been described in the literature.[30] An assessment of upper incisor proclination was therefore undertaken in our study. Our study revealed that only 8.5% of SCD patients had proclined upper incisors. This could be because majority of SCD patients in our study did not have maxillary prognathism.

Conclusion

The average incisal overjet was 3±1.9mm. The mean values obtained for SCD patients in various cephalometric parameters measured did not vary much when compared to cephalometric norms for Ghanaians described in other studies. The prevalence of maxillary protrusion (gnathopathy) in SCD patients in Ghana is 18.1%. However, comparisons could not be made with the general Ghanaian population as prevalence rates for maxillary protrusion in the general population has not yet been assessed. A study on the prevalence of gnathopathy in the Ghanaian population is recommended. This will help in the comparison of prevalence between groups of interest and the general Ghanaian population.

Conflict of interest

Authors declare that they have no competing interest.

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