Original Article

The Cleft Palate Craniofacial Journal
2023, Vol. 60(1) 55-62

DOI: 10.1177/10556656211053154
journals.sagepub.com/home/cpc
SAGE

# Facial and Cephalometric Features of Individuals With Mucopolysaccharidosis: A Cross-Sectional Study

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## Abstract

*Objective:* The aim was to assess craniofacial features through facial anthropometric and lateral cephalometry measurements of individuals with mucopolysaccharidosis (MPS) and compare them with individuals without MPS.

*Design:* Cross-sectional study.

*Patients:* A total of 14 individuals with MPS and 28 non-MPS age- and sex-matched were enrolled in this study.

*Methods:* A clinical facial analysis to evaluate the soft tissues and cephalometric analysis that comprised linear and angular measurements were performed. The calculation of the method error suggested no systematic errors ($p > .05$). Random errors for linear and angular measurements were low (less than 0.5° and 1.6 mm). Chi-square test and independent *t-test* were performed.

*Results:* Most individuals with MPS were dolichofacial, presented altered facial proportions with an increased anterior lower facial height (ALFH) and lip incompetence (all $p < .05$), when compared with non-MPS individuals. Six angular measurements (1s.Na, 1s.NB, FMA, IMPA, AFI, and Po.Or_Go.Me; all $p < .05$) were significantly increased among individuals with MPS, and two (1s.1i and Ba.N-Ptm.Gn, all $p < .05$) were significantly decreased among them. Four linear measurements were significantly increased among individuals with MPS (1s-NA, 1i-NB, S-UL, and S-LL; all $p < .05$) and five (PogN-Perp, Co-A, Co-Gn, Nfa-Nfp, and overbite; all $p < .05$) were significantly decreased among them.

*Conclusion:* In summary, most individuals with MPS were dolichofacial with increased ALFH. Proclined upper and lower incisors, reduced nasopharyngeal space, and reduced overbite was also noted.

## Keywords

mucopolysaccharidoses, rare diseases, malocclusion, cephalometry, dental care for disabled

## Introduction

Mucopolysaccharidosis (MPS) are a group of rare and inherited metabolic disorders, with an estimated incidence of 1 in 22 000 individuals, caused by the accumulation of the glycosaminoglycans (GAGs) inside lysosomes resulting in progressive and systemic clinical manifestations that may take place among MPS individuals (Giugliani, 2012). Affected individuals may have altered dental and craniofacial characteristics. Studies evaluating oral health characteristics among individuals with MPS showed that this group is at a higher risk of developing dental caries and gingivitis (Prado et al., 2019). They may also present enamel defects, macroglossia, tooth eruption delay, and malocclusion traits (Ribeiro et al., 2015; Carneiro et al., 2017).

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Studies on facial and cephalometric features of MPS are scarce in the literature (Fonseca et al., 2014; Ribeiro et al., 2015). The existing evidence suggests that these individuals have an increased anterior lower facial height, convex profile, a tendency towards dolichocephaly, and a narrow nasopharyngeal airway, predisposing them to mouth breathing (Fonseca et al., 2014; Ribeiro et al., 2015). However, no studies have simultaneously analysed soft tissues and cephalometric measurements in individuals with MPS. As soft tissue characteristics are not always linked to underlying matching skeletal features, it is important to quantify differences in the magnitude of the skeletal versus soft tissue disharmonies. Additionally, craniofacial cephalometry is not always available; thus, a good understanding of the facial and dental features is important during the orthodontic management of individuals with MPS.

Considering the entire list of oral manifestations that can affect individuals with MPS, it is important to establish parameters for the surveillance of these patients to prevent or minimize the burden that such oral problems might cause. Awareness of these individuals' most relevant facial and/or cephalometric features may assist oral health care providers in the early diagnosis and treatment planning for oral health issues.

The purpose of the study was to assess simultaneously facial (through direct measurements) and lateral cephalometric features of individuals with MPS and to compare with a matched group of non-MPS individuals.

## Methods

### Editorial Policies and Ethical Considerations

The Research Ethics Committee approved the study of the *Universidade Federal de Minas Gerais* (protocol number 01480212.4.0000.5149). The MPS and non-MPS individuals along with parents/caregivers received a previous explanation concerning the aim of the study. Those who agreed to participate were instructed to sign an informed consent.

The reporting of this article complies with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2008).

### Recruitment of Participants and Setting

A cross-sectional study with a sample of MPS and non-MPS individuals between five and 26 years was conducted. The study group consisted of 14 individuals with MPS recruited from two public hospitals of Belo Horizonte city, Minas Gerais, Brazil, where comprehensive health care for individuals with this condition is provided. MPS individuals who had already undergone orthodontic treatment and those who were uncooperative during the clinical or radiographic examination were excluded from the study. The non-MPS group consisted of 28 individuals who had a routine appointment scheduled in the outpatient clinic of the same hospitals. Non-MPS individuals who had already undergone orthodontic treatment and those who presented any systemic disorder, craniofacial anomalies, or syndromes were excluded. Those who agreed to participate were instructed to schedule an appointment at the Faculty of Dentistry of the *Universidade Federal de Minas Gerais*, where the MPS and non-MPS individuals underwent facial analysis and radiographic examination. Radiographic examinations were performed as an integral part of a treatment plan. All patients had some occlusal alteration, and after data collection, they were referred to orthodontic treatment for evaluation and treatment. MPS and non-MPS individuals were matched by sex and age (1:2). Data collection took place between January 2015 and December 2017.

### Data Collection

*Classification of MPS.* Individuals with MPS were classified according to the type of defective enzyme involved in the breakage pathway of GAGs: MPS I (Hurler; Hurler-Scheie); MPS II (Hunter); MPS III (Sanfillipo); MPS IV (Morquio); MPS VI (Maroteaux-Lamy); MPS VII (Sly); and MPS IX (Natowicz) (Giugliani, 2012). Data were obtained through the report of the parents/caregivers.

*Facial Analysis.* A clinical facial analysis to evaluate the soft tissues was conducted (Farkas, 1994; Suguino et al., 1996; Reis et al., 2006). Chart 1 shows the variables assessed during the facial analysis carried out by one calibrated researcher. The calibration of the researcher was coordinated by an experienced orthodontist, with a doctoral degree and expertise in orthodontic research. The calibration process had two phases. Phase 1 consisted of theoretical training to analyse photographs and to discuss the parameters evaluated (Peres et al., 2001; Oliveira et al., 2008). Phase 2 consisted of the practical exercise. Twenty non-MPS individuals were examined by the researcher–who would collect data–and the expert orthodontist. Inter-examiner agreement between the researcher and the orthodontist was calculated. Twenty individuals were re-examined by the researcher after seven days. Intra-examiner agreement was also calculated.

### Cephalometric Analysis

Radiographic examination was performed as part of a comprehensive oral examination of MPS and non-MPS individuals. Digital lateral cephalograms of the participants were obtained with Kodak 9000C 3D® (Kodak Dental Systems, Carestream Health, USA). This device has a charge-coupled sensor chip working as a receptor of images. For the exposures, the parameters used were 80 kv, 10 mA, and 0.5 s. The same cephalostat was used for all digital exams. Radiographs were obtained with the participants in natural head position, teeth in maximal intercuspation, and lips at rest.

The exams were transferred from their formats and saved as readable files. The cephalometric analysis comprised linear and angular measurements (Tweed, 1953; Steiner, 1960; Rickets et al., 1972; McNamara, 1984). The analyses of the digital lateral cephalograms were performed by a single-blinded oral and maxillofacial radiologist, using Radiocef 6.0 software for

| | | |
|---|---|---|
| Facial Profile | Dolichofacial<br>Mesofacial<br>Brachyfacial | Analysis based on the vertical and horizontal facial pattern.<br>-Dolichofacial: vertical excess of lower facial third and horizontally shortened face.<br>-Brachyfacial: decreased lower facial third and horizontally wider face.<br>-Mesofacial: proportional horizontal and vertical dimensions. |
| Facial proportions | Adequate<br>Inadequate | The vertical height of the middle third of the face (from the supraorbital crest to the base of the nose) should be equal to the height of the lower third (facial thirds should be within a vertical range from 55 to 65 mm). |
| Facial symmetry | Symmetrical<br>Asymmetrical | Symmetry between the right and left sides of the face. Asymmetries of soft orbits, nose, upper lip and mouth ranging between 0.3mm and 1.5mm, and between halves of the mouth reaching almost 5mm, do not present an aesthetic problem. |
| Facial convexity | Straight<br>Concave<br>Convex | Angle formed by the soft tissue of the *Glabella*, subnasal and soft tissue from the *Pogonion*. An average measurement of 11 to 12 degrees suggests the ideal anteroposterior position of the chin. A larger angle indicates mandibular retrognathism (convex), and a smaller one mandibular prognathism (concave). |
| Nasolabial angle | Adequate<br>Acute<br>Obtuse | Formed by the intersection of the upper lip line and the columella to *Subnasale* line (desirable to be between 85 ° to 105°). |
| Anterior lower facial height (ALFH) | Adequate<br>Reduced<br>Increased | Obtained by the distance from Subnasale to Menton points.<br>The face is divided into three vertical thirds which are within a range of 55 to 65mm. ALFH should be equal to the middle third facial height. |
| Lip incompetence | Presence<br>Absence | Presence of passive or active lip sealing. |
| Chin projection | Adequate<br>Shortened<br>Elongated | Formed by the intersection of the neck and submandibular region lines to the chin. The length should be approximately 40 mm ± 5 mm. |

**Chart 1.** Measurement definitions to evaluate soft tissues.

Windows (Radio Memory, Ltda, Belo Horizonte, Brazil). The operator identified the landmarks, and the software automatically calculated the linear and angular measurements.

The error of the method was assessed using 15 randomly selected cephalograms of individuals without any disabilities. The cephalograms were traced and retraced by the same radiologist within 15 days. The systematic error for all quantitative variables (angular and linear cephalometric measures) was assessed with the paired *t*-test. The random error was evaluated using Dahlberg's formula (Dahlberg, 1940).

## Pilot Study

Before the main study, a pilot study was performed. The sample consisted of five individuals with MPS and five non-MPS individuals along with their parents/caregivers. The

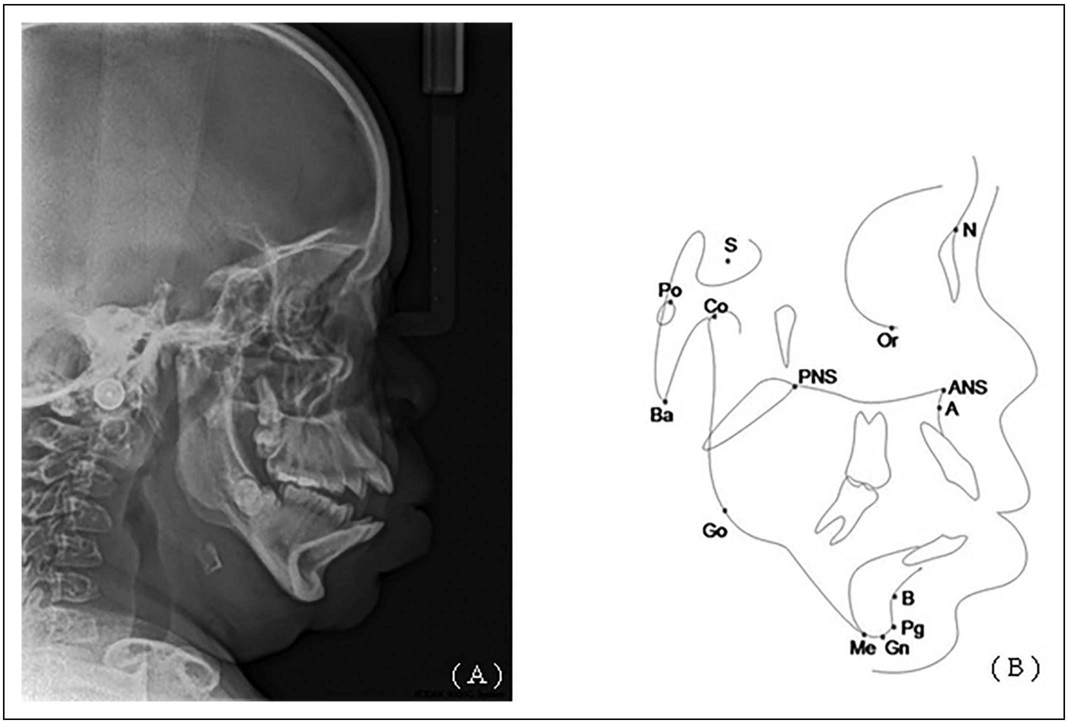


**Figure 1.** (A) Lateral cephalogram showing the skeletal pattern of a 26-year-old female individual with MPS Type VI. (B) Reference points used in cephalometric analysis.

results indicated that changes in the methodological procedures were deemed unnecessary.

### Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS Inc, version 21.0, Chicago, IL, USA). The Fisher's exact test was used to compare MPS and non-MPS participants concerning each variable of the facial analysis. The Shapiro–Wilk test confirmed the normal distribution of quantitative data (linear and angular measurements). The Two-sample Hotelling T-test was performed to determine significant differences regarding the angular and linear measurements between the two groups. The independent *t*-test was used to compare the two groups concerning the angular and linear cephalometric measurements. The level of significance was set at 5%. For each angular and linear cephalometric measurement, the minimum clinically important difference (MCID) was calculated by multiplying the pooled standard deviation (SD) of individuals with MPS and non-MPS by 0.5 (0.5 SD) (Copay et al., 2007).

## Results

### Anthropometric Measurement Reliability

Kappa values for calculating inter-and intra-examiner agreement ranged between 0.76 and 0.98, which were very good (Rigby, 2000). The 20 individuals involved in the calibration process did not participate in the main study.

### Lateral Cephalometry Measurement Reliability

The paired *t-test* showed that all quantitative variables (angular and linear cephalometric measures) had no systematic errors ($p > .05$). The random error was evaluated using Dahlberg's formula (Dahlberg, 1940). The random error ranged between 0.03 mm and 1.59 mm for linear measurements and between 0.03 degrees and 0.51 degrees for angular measurements.

### Participants' Characteristics

Among the 42 participants, 24 (57.1%) were female and 18 (42.9%) were male. Participants' mean age was 13.9 years (±7.2). Regarding the type of MPS, the 14 individuals with MPS were classified as follows: MPS I ($n = 4$), MPS II ($n = 2$), MPS III ($n = 0$), MPS IV ($n = 1$), and MPS VI ($n = 7$). Figure 1 shows the digital lateral cephalogram of an individual with MPS Type VI (A) and the landmarks used in the cephalometric analysis (B).

### Facial Analysis

In comparison with non-MPS individuals, most individuals with MPS were dolichofacial ($p = .001$), had inadequate facial proportions ($p < .001$), increased ALFH ($p < .001$), and absence of lip sealing ($p = .003$). No significant difference between groups was found for facial symmetry, profile, nasolabial angle, and chin projection (Table 1).

**Table 1.** Facial Analysis of Individuals with and Without MPS ($n = 42$).

| | Individuals with MPS (%) | Individuals without MPS (%) | *p* value* |
|---|---|---|---|
| **Facial type** | | | |
| Dolichofacial | 13 (92.9) | 10 (35.7) | <.001 |
| Mesofacial | 1 (7.1) | 7 (25.0) | |
| Brachyfacial | 0 | 11 (39.3) | |
| **Facial symmetry** | | | |
| Symmetrical | 13 (92.9) | 25 (89.3) | 1.000 |
| Asymmetrical | 1 (7.1) | 3 (10.7) | |
| **Profile** | | | |
| Straight | 2 (14.3) | 1 (3.6) | .696 |
| Concave | 0 | 5 (17.9) | |
| Convex | 12 (85.7) | 22 (78.6) | |
| **Facial proportions** | | | |
| Adequate | 0 | 18 (64.3) | <.001 |
| Inadequate | 14 (100.0) | 10 (35.7) | |
| **Nasolabial angle** | | | |
| Adequate | 11 (78.6) | 26 (92.9) | .312 |
| Open | 1 (7.1) | 2 (7.1) | |
| Closed | 2 (14.3) | 0 | |
| **Anterior Lower Facial Height (ALFH)** | | | |
| Adequate | 0 | 18 (64.3) | <.001 |
| Reduced | 1 (7.1) | 2 (7.1) | |
| Increased | 13 (92.9) | 8 (28.6) | |
| **Lip sealing** | | | |
| Presence | 7 (50.0) | 26 (92.9) | .003 |
| Absence | 7 (50.0) | 2 (7.1) | |
| **Chin projection** | | | |
| Adequate | 13 (92.9) | 26 (92.9) | 1.000 |
| Shortened | 1 (7.1) | 0 | |
| Elongated | 0 | 2 (7.1) | |

*Fisher's exact test. Statistical significance $p < .05$.

## *Analysis of Angular and Linear Cephalometric Measurements*

Table 2 displays the comparisons between individuals with MPS and non-MPS for the angular measurements. The Two-sample Hotelling T-test showed that there was a significant difference $F$ (13.28) = 8.54, $p < .001$ of the mean angular measurements between the two groups.

The following angular measurements were significantly higher among individuals with MPS in comparison with non-MPS individuals: 1s.Na (10.51°; $p = .002$), 1s.NB (20.24°; $p < .001$), FMA (11.46°; $p < .001$), IMPA (13.58°; $p < .001$), AFI (12.22°; $p < .001$), and Po.Or_Go.Me (11.46°; $p < .001$). The following angular measurements were significantly lower among individuals with MPS than in non-MPS individuals: 1s.1i (33.09°; $p < .001$) and Ba.N-Ptm.Gn (4.02°; $p = .026$). The mean difference between groups was higher than the MCID for all angular measurements, except for the AFI.

Table 3 displays the comparison of linear cephalometric measurements between individuals with MPS and non-MPS. The Two-sample Hotelling T-test showed that there was a significant difference $F(14,27) = 11.56$, $p < .001$ in the mean linear measurements between the two groups. The results showed that four linear measurements were significantly higher among individuals with MPS in comparison with non-MPS individuals: 1s-NA (15.67 mm, $p = .001$), 1i-NB (21.79 mm, $p = .001$), S-UL (23.28 mm, $p < .001$), and S-LL (31.91 mm, $p < .001$). The following linear measurements were significantly lower among individuals with MPS: PogN-Perp (26.66 mm, $p = .001$), Co-A (38.52 mm; $p = .020$); Co-Gn (42.97 mm; $p = .041$); Nfa-Nfp (16.71 mm, $p = .001$), and overbite (16.05 mm, $p = .003$). The mean difference between groups was higher than the MCID for all linear measurements.

## *Calculation of Sample Power*

The calculation of sample power was carried out with the Power and Sample Size Calculation online software (PS, version 3.0; Nashville, TN, USA). Three angular measurements [IMPA (Tweed, 1953), 1s.NB (Steiner, 1960), and

**Table 2.** Comparison of Angular Cephalometric Measurements Between Individuals with and Without MPS ($n = 42$).

| | Individuals with MPS | | Individuals without MPS | | | | | |
|---|---|---|---|---|---|---|---|---|
| Angular Measurements (°) | Mean | *SD* | Mean | *SD* | *t* value | *p* value* | Mean angular difference | MCID 0.5 (*SD*) |
| SNA | 81.69 | 5.56 | 81.89 | 6.14 | −0.10 | = .917 | 0.2 | 2.94 |
| SNB | 77.47 | 4.06 | 78.94 | 4.50 | −0.10 | = .310 | 1.5 | 2.18 |
| ANB | 4.22 | 3.88 | 2.95 | 3.97 | 0.98 | = .333 | 1.27 | 1.97 |
| SN.GoGn | 39.98 | 8.29 | 32.94 | 7.35 | 2.80 | = .008 | 7.04 | 4.14 |
| SNGn | 69.04 | 4.72 | 67.95 | 4.33 | 0.74 | = .462 | 1.09 | 2.22 |
| 1s.Na | 35.02 | 12.21 | 24.51 | 7.83 | 3.38 | = .002 | 10.51 | 5.31 |
| 1s.NB | 44.74 | 12.39 | 24.50 | 7.43 | 6.62 | <.001 | 20.24 | 6.67 |
| 1s.1i | 96.01 | 19.63 | 129.20 | 13.2 | −6.45 | <.001 | 33.19 | 11.08 |
| FMA | 36.60 | 7.74 | 25.14 | 5.97 | 5.30 | <.001 | 11.46 | 4.25 |
| IMPA | 103.8 | 11.08 | 90.22 | 8.74 | 4.33 | <.001 | 13.58 | 5.79 |
| AFI | 59.02 | 5.58 | 46.80 | 4.43 | 8.92 | <.001 | 12.22 | 18.32 |
| Po.Or_Go.Me | 36.60 | 7.74 | 25.14 | 5.97 | 5.30 | <.001 | 11.46 | 4.25 |
| Ba.N-Ptm.Gn | −6.66 | 5.23 | −2.61 | 5.40 | −2.31 | = .026 | 4.05 | 2.81 |

*Independent *t* test ($p < 0.05$)/ MCID, minimal clinically important difference; SD, standard deviation.

**Table 3.** Comparison of Linear Cephalometric Measurements Between Individuals with and Without MPS ($n = 42$).

| | Individuals with MPS | | Individuals without MPS | | | | | |
|---|---|---|---|---|---|---|---|---|
| Linear Measurements (mm) | Mean | *SD* | Mean | *SD* | *t* value | *p* value* | Mean linear difference | MCID 0.5 (*SD*) |
| 1s-NA | 29.78 | 15.56 | 14.11 | 11.60 | 3.67 | =.001 | 15.67 | 7.43 |
| 1i-NB | 36.75 | 14.01 | 14.96 | 9.28 | 6.02 | =.001 | 27.79 | 7.53 |
| S-L | 116.21 | 24.91 | 131.78 | 43.46 | −1.23 | =.223 | 15.57 | 19.33 |
| S-UL | 20.66 | 14.86 | −2.62 | 13.52 | 5.09 | <.001 | 23.28 | 8.88 |
| S-LL | 29.99 | 24.45 | −1.92 | 25.61 | 3.86 | <.001 | 31.91 | 14.60 |
| AN-Perp | −2.89 | 17.83 | 4.56 | 12.56 | −1.57 | =.123 | 7.45 | 7.37 |
| PogN-Perp | −26.98 | 30.15 | −0.32 | 18.07 | −3.58 | =.001 | 26.66 | 12.89 |
| Co-A | 190.97 | 31.01 | 229.49 | 54.98 | −2.42 | =.020 | 38.52 | 25.65 |
| Co-Gn | 260.48 | 39.82 | 303.45 | 70.26 | −2.11 | =.041 | 42.97 | 32.30 |
| Nfa-Nfp | 19.99 | 10.24 | 36.70 | 15.48 | −3.64 | =.001 | 16.71 | 7.98 |
| Bfa-Bfp | 31.21 | 10.07 | 31.78 | 8.92 | −0.18 | =.855 | 0.57 | 4.6 |
| ENA-Me | 185.16 | 28.87 | 180.30 | 40.39 | 0.40 | =.691 | 4.86 | 18.33 |
| Overbite | −14.49[a] | 22.54 | 1.56 | 6.85 | −3.26 | =.003 | 16.05 | 6.91 |
| Overjet | 6.13[a] | 6.91 | 8.28 | 8.60 | −0.643 | =.525 | 2.15 | 4.09 |

*Independent *t* test ($p < 0.05$).
a$n = 8$/MCID, minimal clinically important difference; SD, standard deviation.

Po.Or_Go.Me (McNamara, 1984)] and two linear measurements [1i-NB (Steiner, 1960) and Nfa-Nfp (McNamara, 1984)] were chosen. For each measurement, mean differences and the pooled standard deviation were calculated for the determination of the power. A type I error of 5% was adopted.

The mean differences (pooled standard deviation) for angular measurements were: IMPA = 13.57 (11.45), 1s.NB = 20.24 (13.35), and Po.Or_Go.Me = 11.46 (8.51). The values of the power of the sample were: IMPA = 94.1%, 1s.NB = 99.4%, and Po.Or_Go.Me = 97.9%.

The mean differences (pooled standard deviation) for linear measurements were: 1i-NB = 27.79 (15.07) and Nfa-Nfp = 16.71 (15.96). The values of the power of the sample were: 1i-NB = 99.9% and Nfa-Nfp = 87.7%.

## Discussion

In the present study, individuals with MPS presented themselves predominantly as dolichofacial individuals, with increased ALFH and lip incompetence when compared to non-MPS individuals. The dolichofacial pattern associated with the increased ALFH in individuals with MPS might be explained by the occurrence of dysostosis (a condition that alters bone growth) and the presence of an enlarged cranium, which is a consequence of the disease (Valayannopoulos et al., 2010).

The constant accumulation of GAGs in the airway cells of MPS individuals can also lead to mouth breathing, which, ultimately, leads to lip incompetence. Simmons et al., (2005) described that GAGs accumulation can lead to the hypertrophy of tonsils or may distend pharyngeal walls, causing partial airway obstruction. The literature shows that when the nostrils are blocked, individuals develop mouth breathing to facilitate the flow of air into the expanding lungs and increased activity of the muscles of the face, lips, and tongue are observed (Harvold et al., 1981). Therefore, the presence of facial deformities, open bite, and lip incompetence can be developed based on the changes in the functional matrix. In addition to airway obstruction, macroglossia may also contribute to the development of mouth breathing. A previous study performed with 26 individuals with MPS in the Northeast of Brazil also showed that clinically, most individuals presented with midface deficiency, increased ALFH, anterior open bite, a convex profile, and macroglossia (Ribeiro et al., 2015). However, this study did not evaluate cephalometric measurements simultaneously with facial and clinical analysis. Clinicians must be aware of these two existing parameters to guide orthodontic diagnosis and tooth movement decisions. It is not always possible to establish a match between both parameters, as soft tissue thickness can camouflage or increase the measured differences in skeletal and dental variables.

Angular and linear cephalometric measurements showed that most individuals with MPS had pro-inclined upper and lower incisors, and as a consequence, protrusive upper and lower lips when compared to non-MPS individuals. Pro-inclination of incisors may be associated with the presence of macroglossia. Macroglossia is a marked characteristic among individuals with MPS (Torres et al., 2018a). The literature has indeed recognized that the tongue's posture and size may significantly influence tooth position (Torres et al., 2018b).

Most individuals with MPS also had a clockwise mandibular growth and an increased ALFH. The measurements of FMA were significantly higher among MPS individuals, indicating that the inclination of the mandible plan had a growth pattern in the vertical direction. This cephalometric result was confirmed by the facial analysis performed in the present study. Fonseca et al., (2014) presented similar results. They stated that individuals with MPS tend to a vertical growth that results in a dolichofacial pattern. In the present study, the statistical differences were also clinically significant, confirming the importance of orthodontic evaluation and intervention in individuals with MPS as early as possible to minimize maxillary and/or mandibular discrepancies.

Some studies have shown that because of the accumulation of GAGs in the upper airway and the eventual upper airway obstruction, individuals with MPS face many airway issues, such as obstructive sleep apnea (OSA) and frequent respiratory infections (Simmons et al., 2005; Gönüldaş et al., 2014). In the present study, a significant reduction of the Nfa-Nfp linear measurement among individuals with MPS was observed, which means that these individuals may have a reduced nasopharyngeal space. However, the results of Nfa-Nfp presented herein must be evaluated with caution, as they were done with the use of a 2D tool. Further studies using 3D airway measures to assess the nasopharyngeal function are recommended**.**

Reduced measurements of overbite were observed among the group with MPS and it may be explained by the reduced nasopharyngeal space and obstruction of the upper airway. These factors may have implications for mouth breathing, and consequently, for a higher prevalence of open bite. Moreover, macroglossia influences tooth position, tooth pro-inclination, and open bite (Torres et al., 2018b). A Brazilian cross-sectional study found similar results and showed that 50% of 17 individuals with MPS evaluated were diagnosed with anterior open bite. Moreover, macroglossia and hypoplastic mandibular condyle were also observed among individuals with MPS (Almeida-Barros et al., 2018).

Some limitations of the present study should be acknowledged. The first is inherent to the design of a cross-sectional study that cannot assess causality. The use of a 2D lateral cephalometric analysis to measure nasopharyngeal space may also represent a downside as it can cause geometric distortion or superimposition of structures. Still, it can be considered a starting point for future studies regarding craniofacial features in individuals with MPS. Finally, it is important to highlight that the sample size was not calculated. The low overall prevalence of MPS makes the recruitment of a large sample quite challenging. Thus, data collection was conducted in a reference center where health care for individuals with MPS is provided.

The present study suggests statistical and clinically noticeable differences in facial and cephalometric measurements between MPS and non-MPS individuals. For most analysed variables in our study, the statistical differences between MPS and non-MPS individuals were higher than the MCID. This demonstrates that the changes found were indeed clinically significant. The major differences were observed in the angular variables 1.1si [33.19°] and 1s.NB [20.24°] and in the linear variables CoA [38.52 mm] and CoGn [42.97 mm]. The presence of considerable linear and angular differences between groups shows the great disharmony in the facial bones of individuals with MPS, which may lead to the significant aesthetic and functional impact caused by the syndrome.

## Conclusion

Facial and cephalometric differences were observed between MPS and non-MPS groups. Most individuals with MPS were dolichofacial with significantly increased anterior lower facial height and major open bite, with severely proclined upper and lower incisors and reduced nasopharyngeal space. The magnitude of the identified differences was quite large (more than 10 degrees or 10 mm of difference) with clear clinical relevance.

## Authors' Contribution

N. C. R. Carneiro participated in the project's conception and design, acquisition of data, analysis and interpretation of data, and writing the article. L. G. Abreu collaborated in the analysis and interpretation of data, writing and critical revision of the article. R. M. C. Milagres collaborated in the analysis and interpretation of data. T. M. P. Amaral collaborated in the analysis and interpretation of data. C. Flores-Mir collaborated in the writing and critical revision of the article. I. A. Pordeus participated in the project's conception and design and critical revision of the article. A. C. Borges-Oliveira participated in the project's conception and design, analysis and interpretation of data, and critical revision of the article.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001; Conselho Nacional de Desenvolvimento Científico e Tecnológico-Brasil (CNPq); Fundação de Amparo à Pesquisa do Estado de Minas Gerais- Brasil (FAPEMIG); and Pró-Reitoria de Pesquisa da Universidade Federal de Minas Gerais (PRPq/UFMG).

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### Supplemental Material

Supplemental material for this article is available online.

### References

Almeida-Barros RQ, Medeiros PFV, Azevedo MQA, Oliveira Lira Ortega A, Yamamoto ATA, Dornelas SKL, Bento PM. Evaluation of oral manifestations of patients with mucopolysaccharidosis IV and VI: clinical and imaging study. *Clin Oral Investig*. 2018;22(1):201-208.

Carneiro NCR, Deps TD, França EC, Valadares ER, Pordeus IA, Borges-Oliveira AC. Oral health of children and adolescents with mucopolysaccharidosis and mother's sense of coherence. *Spec Care Dentist*. 2017;37(5):223-229.

Copay AG, Subach BR, Glassman SD, Polly DWJr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J*. 2007;7(5):541-546.

Dahlberg G. *Statistical methods for medical and biological students*. London: George Allen and Unwin; 1940:122-132.

Farkas LG. Examination. In: Farkas LG, ed. *Anthropometry of the head and face*, 2nd ed. New York: Raven Press; 1994:30-56.

Fonseca FRA, Sarmento DJS, Medeiros PFV, Diniz DN, Santos MTBR. Patients with mucopolysaccharidosis have tendencies towards vertical facial growth. *J Oral Maxillofac Surg*. 2014;72-(12):2539-2546.

Giugliani R. Mucopolysaccharidosis: from understanding to treatment, a century of discoveries. *Genet Mol Biol*. 2012;35(4):924-931.

Gönüldaş B, Yilmaz T, Sivri HS, Güçer KŞ, Kılınç K, Genç GA, Kılıç M, Coşkun T. Mucopolysaccharidosis: otolaryngologic findings, obstructive sleep apnea and accumulation of glucosaminoglycans in lymphatic tissue of the upper airway. *Int J Pediatr Otorhinolaryngol*. 2014;78(6):944-949.

Harvold EP, Tomer BS, Vargervik K, Chierici G. Primate experiments on oral respiration. *Am J Orthod*. 1981;79(4):359-372.

McNamara JAAJr. A method of cephalometric evaluation. *Am J Orthod*. 1984;86 (6):449-469.

Oliveira AC, Czeresnia D, Paiva SM, Campos MR, Ferreira EF. Utilization of oral health care for down syndrome patients. *Rev Saude Publica*. 2008;42(4):693-699.

Peres MA, Traebert J, Marcenes W. Calibration of examiners for dental caries epidemiology studies. *Cad Saude Publica*. 2001;17-(1):153-159.

Prado HV, Carneiro NCR, Perazzo MF, de Abreu MHNG, Martins CC, Borges-Oliveira AC. Assessing a possible vulnerability to dental caries in individuals with rare genetic diseases that affect the skeletal development. *Orphanet J Rare Dis*. 2019;14(1):145.

Reis SAB, Abrão J, Capelozza FL, Claro CAA. Subjective facial analysis. *R Dental Press Ortodon Ortop Facial*. 2006;11(5):159-172.

Ribeiro EM, Fonteles CSR, Freitas AB, Alves KSS, Monteiro AJ, Silva CAB. A clinical multicenter study of orofacial features in 26 Brazilian patients with different types of mucopolysaccharidosis. *Cleft Palate Craniofac J*. 2015;52(3):352-358.

Rickets RM, Bench RW, Hilgers JJ, Schulhof AB. An overview of computerized cephalometrics. *Am J Orthod*. 1972;61(1):1-28.

Rigby AS. Statistical methods in epidemiology. Towards an understanding of the kappa coefficient. *Disabil Rehabil*. 2000;22-(8):339-344.

Simmons MA, Bruce IA, Penney S, Wraith E, Rothera MP. Otorhinolaryngological manifestations of the mucopolysaccharidoses. *Int J Pediatr Otorhinolaryngol*. 2005;69(5):589-595.

Steiner CC. The use of cephalometrics as an aid to planning and assessing orthodontic treatment. *Am J Orthod*. 1960;46(10):721-735.

Suguino R, Ramos AL, Terada HH, Furquim LZ, Maeda L, Silva Filho OG. Facial analysis. *R Dental Press Ortodon Ortop Facial*. 1996;1(1):86-107.

Torres RO, Pintor AVB, Guedes FR, Freitas-Fernandes LB, Barth AL, Horovitz DDG, de Souza IPR. Oral and craniofacial manifestations in a hunter syndrome patient with hematopoietic stem cell transplantation: a case report. *Spec Care Dentist*. 2018a;38(1):51-54.

Torres RO, Pintor AVB, Guedes FR, Cevidanes LHS, Freitas-Fernandes LB, de Oliveira Ruellas AC, de Souza IPR. Three-dimensional dental and craniofacial manifestations in patients with late diagnosis of mucopolysaccharidosis type II: report of 2 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018b;16:S2212-S4403(18)30883–6.

Tweed CH. Evolutionary trends in orthodontics- past, present, and future. *Am J Orthod*. 1953;39(2):81-108.

Valayannopoulos V, Nicely H, Harmatz P, Turbeville S. Mucopolysaccharidosis VI. *Orphanet J Rare Dis*. 2010;5:5.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349.