Morphometric Characterization of Asymmetric Mandibles Due to Condylar Hyperactivity

*Sebastian Espinosa, DDS, OMS, **

Carolina Rabanal, DDS,† and Viviana Toro-Ibacache, DDS, MSc, PhD‡

Purpose: Mandibular asymmetry related to condylar hyperactivity (CH) presents a complex set of morphologic features that pose challenges for its correction. Using state-of-the-art morphometric techniques, this report provides a detailed and hierarchical description of the features present in CH-related asymmetric mandibles and offers new knowledge for the surgical treatment of CH.

Materials and Methods: Sixty patients were included in the sample. Thirty had CH-related asymmetric mandibles and the other 30 had clinically symmetric mandibles. Twenty-eight 3-dimensional landmarks were placed on computed tomographically based reconstructions of each participant's mandible and analyzed using geometric morphometric analysis for the quantitative and qualitative comparison of their morphologic features.

Results: All 60 participants exhibited asymmetry. However, those with CH exhibited a broad range of shapes and even shared several morphologic features with the controls. Mainly the ramus and then the body were the main contributors of the differences between groups.

Conclusions: There is considerable overlap of anatomic features characterizing symmetric and asymmetric mandibles; based on shape alone, the 2 groups can be easily misclassified. The ramus and body of the affected side in CH-related asymmetric mandibles were the main contributors to asymmetry of the structure. The chin, a usual diagnostic structure, did not greatly contribute to the structural asymmetry of the mandible.

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J Oral Maxillofac Surg 77:1056-1067, 2019

Mandibular asymmetries are a constant challenge for surgeons in terms of surgical planning. Because many structures can be affected, making surgical decisions can be difficult. Surgical correction of the asymmetry is not merely a matter of aligning all structures of the mandible to the midsagittal plane. The surgeon must understand the normal ranges of shape variation of the mandible to accurately detect the most compromised areas in need of surgical correction. Four main geometric features are involved in the resolution of mandibular asymmetries: orientation, size, position, and shape.[1] From a morphometric perspective, shape is defined as the residual information found when scaling, positioning, and rotation of specimens in a sample are eliminated.[2,3] In some cases, the orientation and position of the mandible in relation to the midsagittal plane are sufficient to obtain acceptable results. In others, correcting all 4 features might be necessary. The contour and presence of transversal and vertical asymmetries play important roles in the shape of the

*Attending Surgeon, Department of Oral and Maxillofacial Surgery, Hospital Sótero del Río, Santiago, Chile.

†Attending Radiologist, Department of Oral and Maxillofacial Radiology, Hospital Sótero del Río, Santiago, Chile.

‡Researcher, Centro de Análisis Cuantitativo en Antropología Dental, Facultad de Odontología, Universidad de Chile, Santiago, Chile; Researcher, Department of Human Evolution, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany.

Address correspondence and reprint requests to Dr Espinosa: Servicio de Cirugía Maxilofacial, Hospital Sotero del Río, Av Concha y Toro 3456 Zip Code: 8150013, Puente Alto, Santiago, Chile; e-mail: sebastianespinosas@gmail.com

mandible, with or without a marked degree of clinical asymmetry. Understanding the morphologic features that are compromised in mandibular asymmetries and the extent of their alterations can provide more diagnostic information to correct them in a predictable way.

A common cause of mandibular asymmetry is condylar hyperactivity (CH). This entity has been described since 1873[4] and consists of idiopathic growth of 1 condylar process of the mandible. The consequence of this growth is progressive deviation of the mandible to the unaffected side. Obwegeser and Makek[5] proposed a simple and practical classification of CH based on clinical, histologic, and linear measurements on orthopantomograms (OPGs). They proposed 3 types of growth: a horizontal pattern (hemimandibular elongation [HE]), a vertical pattern (hemimandibular hyperplasia [HH]), and mixed forms. Although this classification has been useful, OPGs are not always reliable when performing detailed measurements of mandibular asymmetries.[6-12] This is explained by the imaging method on which the OPG is based. Because the mandible presents a rather complex 3-dimensional (3D) anatomy, OPGs should be used with caution for measurements, diagnosis, or surgical decision making. Indeed, Nitzan et al[13] performed clinical and radiologic evaluations of 61 patients and did not find a correlation with the characteristics described by Obwegeser and Makek[5] in their clinical and radiologic description. They concluded that *1)* CH can occur at any age; *2)* it does not stop at the end of the growth period; *3)* CH has a female predominance; and *4)* its laterality depends on gender.

Three-dimensional imaging and virtual analysis techniques allow localization and quantification of changes in areas that are more compromised in mandibular deformation.[14-18] This has led to the better understanding, assessment, and diagnosis of facial asymmetries. Among these techniques, computer-assisted surgical simulation (CASS) has greatly helped to improve surgical predictability.[19-21] In the authors' experience, CASS has shown that mandibles differ in their shape alteration, despite patients having the same diagnosis. Knowing in detail how the mandible is deformed during CH not only helps to understand the complex processes that bone undergoes but also provides the basis for the development of new surgical techniques.

As an analytical technique, the authors use 3D geometric morphometric (GM) analysis. GM analysis studies the covariation between changes in biological forms and their underlying factors.[2,3] It has been widely used in morphologic and other biological sciences, but its adoption in the clinic has been rather slow.[22-24] GM tools combined with 3D reconstruction techniques are helpful to visualize and perform quantitative analysis of 3D shape changes. GM analysis consists of 4 fundamental steps: obtaining primary data, obtaining shape variables, statistical analysis, and visualization of shape changes. One principle that rules GM analysis is the use of reliable landmarks that are found at anatomic points. The coordinates of these landmarks correspond to primary data. These undergo Procrustes fit, in which differences among individuals owing to rotation, translation, and size are eliminated. This procedure generates new data (Procrustes coordinates) that represent pure shape and that can be analyzed using multivariate statistics.

The aim of this work was to provide a detailed description of the anatomic features that are commonly affected in CH-related asymmetric mandibles. With that in mind, the authors tested the null hypothesis that there are no differences between CH-related asymmetric mandibles and control mandibles without a CH diagnosis.

Materials and Methods

SAMPLE

A retrospective study was designed with 60 patients who were divided into study and control groups. The study group was composed of 30 patients with mandibular asymmetry associated with active CH who were under clinical and imaging (cone-beam computed tomography [CBCT] and single-photon emission computed tomography) follow-up. The control group was composed of 30 patients from the authors' department who underwent CBCT for other medical reasons unrelated to this study. Mandibular asymmetry was defined as a deviation of the menton (Me) larger than 4 mm from the midsagittal facial plane constructed with CBCT and ProPlan CMF (ProPlan CMF 3.0, Materialise, Leuven, Belgium). For the 2 groups, the isotropic voxel size was 0.125 mm. All images were acquired with the same equipment (Galileos Comfort, Dentsply Sirona, York, PA). All participants gave their consent for inclusion in the study. The study was approved by the ethical committee of the Hospital Sótero del Río (Santiago, Chile).

Participants in the control group were included after the assessment of their features by a radiologist and orthodontist (C.R.) using CT-based cephalometric tracings (Rickett analysis). The inclusion criteria were skeletal Class I with no asymmetry (based on the criteria defined earlier) and the absence of vertical anomalies or any other pathology that could affect the morphology of the mandible. The composition of the sample is presented in Table 1.

Three-dimensional reconstructions of the 60 mandibles were prepared using a semiautomatic segmentation algorithm with 3D-Slicer[25] and exported as

Table 1. COMPOSITION OF SAMPLE

	Control Group	Study Group	Total
Men/women (% total)	11/19 (30-70)	10/20 (33-66)	21/39 (35-65)
Age (yr), range (mean)	10-38 (22.8)	15-49 (25.5)	10-49 (24.2)

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

stereolithographic files. Twenty-eight landmarks were placed on the 3D surfaces using Avizo 9.1 (FEI, Hillsboro, OR) to represent *1)* the overall geometry of the mandible and *2)* the most relevant esthetic areas (Fig 1, Table 2). Landmarks were placed by 1 observer (S.E.) at 2 different sessions to assess intraobserver error.

ANALYSES

First, a general Procrustes fit of the 60 landmark configurations was performed, consisting of rotation, translation, and scaling to the same centroid size (a geometric measure of size[2]). The shape variables obtained were studied using first Procrustes analysis of variance (ANOVA), a nested-type of model, to assess *1)* the general effect of the variable under study (CH diagnosis), *2)* gender as a potentially confounding factor, *3)* presence of asymmetry, and *4)* error introduced by the creation of landmarks.[26-28] Second, an exploratory approach (principal components analysis [PCA]) was performed to assess and describe the general patterns of shape

variation present in the sample with respect to mean shape (ie, average of all Procrustes coordinates).

The difference in the mean shape between groups (represented by Procrustes distance) was statistically tested using discriminant function analysis and 10,000 rounds of permutations. In addition, a cross-validation test was performed to assess the reliability of the patients' classification in each group used. Although gender does not act as a confounding factor for shape (see below), it is expected that size alone differs between men and women. Thus, overall size differences among groups were analyzed separately for men and women using the Kruskal-Wallis test and pairwise Mann-Whitney comparison in PAST.[29] The effect of size variation on shape changes (allometry) was tested using multivariate regression of shape components on centroid size and its statistical relevance with 10,000 rounds of permutation. Analyses were performed using MorphoJ[30] with a *P* value less than .05 considered significant.
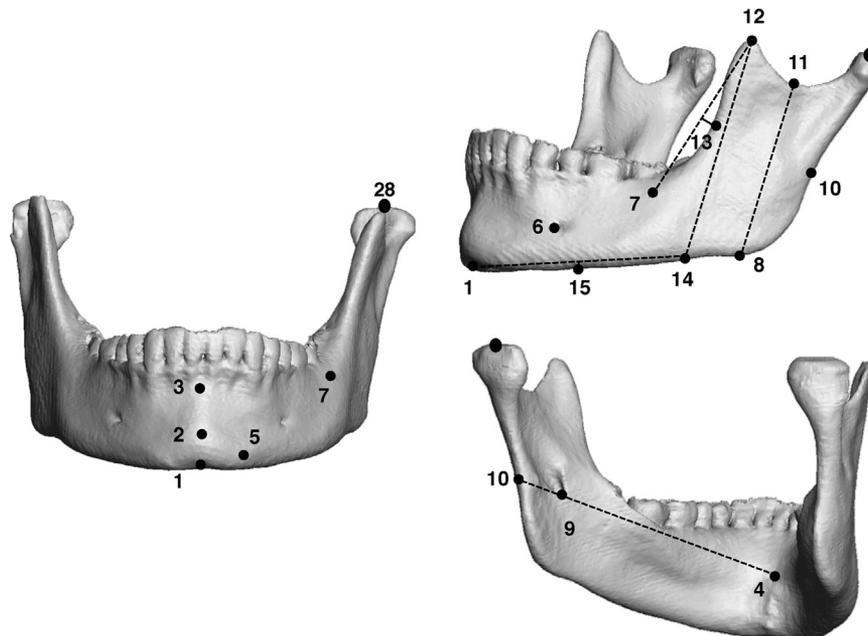

FIGURE 1. Selected landmarks. Only midline and landmarks of the left side are shown for different views of the computed tomographically based 3-dimensional reconstruction. The same landmarks were placed on the right side (not shown). *1,* menton; *2,* pogonion; *3,* point B; *4,* mental spine; *5,* mental protuberance; *6,* mental foramen; *7,* oblique line; *8,* gonion; *9,* mandibular foramen; *10,* ramus posterior; *11,* mandibular notch; *12,* coronoid process; *13,* ramus anterior; *14,* mandibular border 1; *15,* mandibular border 2; *28,* condyle.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

Table 2. LANDMARKS AND DEFINITIONS USED IN THIS STUDY

Number	Landmark	Definition
1	Menton	Most inferior point of mandibular symphysis
2	Pogonion	Most anterior point of triangle delimiting the chin at the mandibular symphysis
3	Point B	Most concave point on the alveolar process below the apex of the roots of the 2 central incisors
4	Mental spines	Superior end between upper mental spines
5 and 16	Mental protuberance	Most lateral end of mental protuberance
6 and 17	Mental foramen	Most anterior point of mental foramen
7 and 18	Oblique line	Point on oblique line (external oblique ridge) at the vestibular tissue of the second molar
8 and 19	Gonion	Most inferior and posterior point of the ramus, when the gonial curvature becomes vertical
9 and 20	Mandibular foramen	Most concave point of the medial border of the mandibular foramen
10 and 21	Ramus posterior	Point at posterior border of the mandibular ramus, on the line passing through mental spines and mandibular foramen
11 and 22	Mandibular notch	Most concave point of mandibular notch
12 and 23	Coronoid process	Tip of coronoid process
13 and 24	Ramus anterior	Point at anterior border of the ramus of the mandible, at half distance between the coronoid process and the temporalis crest
14 and 25	Mandibular border 1	Point at lower border of the body of the mandible, on the line passing through coronoid tip parallel the line linking the gonion and the mandibular notch
15 and 26	Mandibular border 2	Point at lower border of the body of the mandible, at half distance between the menton and mandibular border 1
27 and 28	Condyle	Uppermost point of condyle

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

Visualization of the ranges of shape variation was performed using the surface of the mean shape and the warping vectors from the mean configuration onto the extreme principal component (PC) scores reached by the sample.[2]

To facilitate recognition of the landmarks and structures that contributed most to the observed shape changes in the asymmetric sample, the linear distance of the Procrustes coordinates of each asymmetric mandible to the mean control shape was calculated and plotted.

Results

The Procrustes ANOVA (Table 3) showed that diagnosis and gender had relevant effects on the general variation of the sample (ie, the factor 'individual'). However, diagnosis accounted for 3.14 times the variance caused by differences between men and women. Thus, the sample was pooled in subsequent analyses. There was a marked effect of directional asymmetry (ie, consistent left-vs-right differences; factor "side") and of fluctuating asymmetry. Fluctuating asymmetry and subtle random left-versus-right differences (factor "individual × side") can be considered "natural" errors (signs of developmental instability)[31] owing to the effect of developmental noise. This factor was used to weigh the effect of intra-observer error (factor "double land-marking"), which was negligible.

PCA showed that, with slightly more than 22.63% of the variance explained, the first PC (PC1) separated the sample into CH and control groups (Fig 2). In

Table 3. PROCRUSTES ANALYSIS OF VARIANCE FOR THE EFFECT OF GENDER, ASYMMETRY TYPES, DIAGNOSIS, AND MEASUREMENT ERROR

Effect	Sum of Squares	Mean Squares	Degrees of Freedom	F	P Value
Gender	2.27×10^{-2}	5.68×10^{-4}	40	2.79	<.01
Diagnosis	7.13×10^{-2}	1.78×10^{-3}	40	8.76	<.01
Individual	4.64×10^{-1}	2.04×10^{-4}	2,280	3.53	<.01
Side (directional asymmetry)	6.33×10^{-3}	1.71×10^{-4}	37	2.97	<.01
Individual × side (fluctuating asymmetry)	1.26×10^{-1}	5.77×10^{-5}	2,183	10.98	<.01
Error (repeated land marking)	2.43×10^{-2}	5.25×10^{-6}	4,620		

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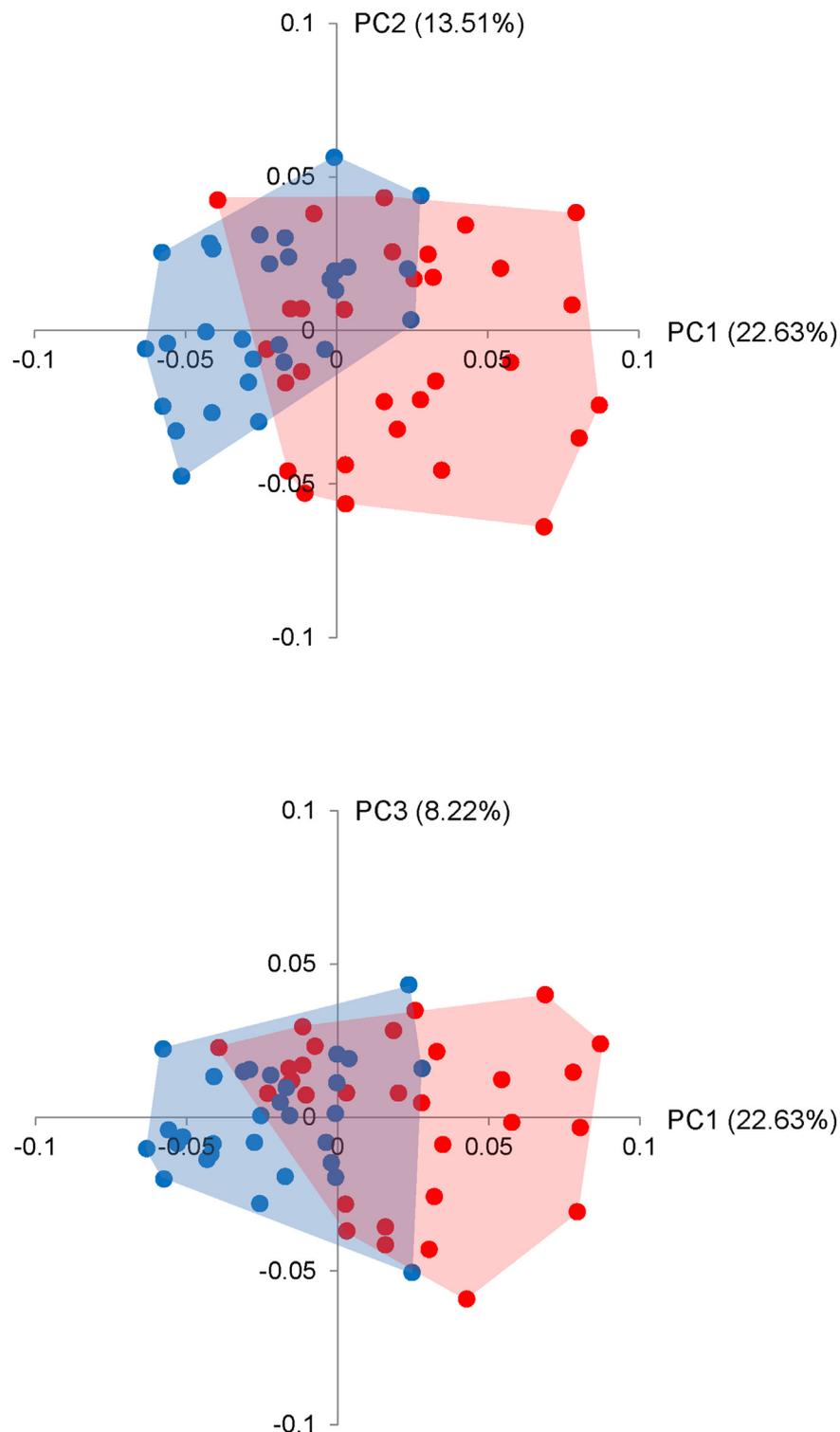
FIGURE 2. Principal components analysis of shape variables. The variance explained by PC1 to PC3 is shown in parentheses. Although there is a distinction between groups, a rather large area of overlap of the symmetric (*blue*) and asymmetric (*red*) groups is evident, implying an important number of features shared by the 2 groups. PC1, principal component 1; PC2, principal component 2; PC3, principal component 3.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

relation to controls, CH-associated mandibles tended to be widely variable, with several reaching the shape variation span of controls (ie, being morphologically similar to controls). For the control group (Fig 3), asymmetric mandibles tended to have the chin deviated to the right side (Fig 3C, D). Also, it was in a lower position and more vertically extended. Its contour also was affected and exhibited a vertical asymmetry. The
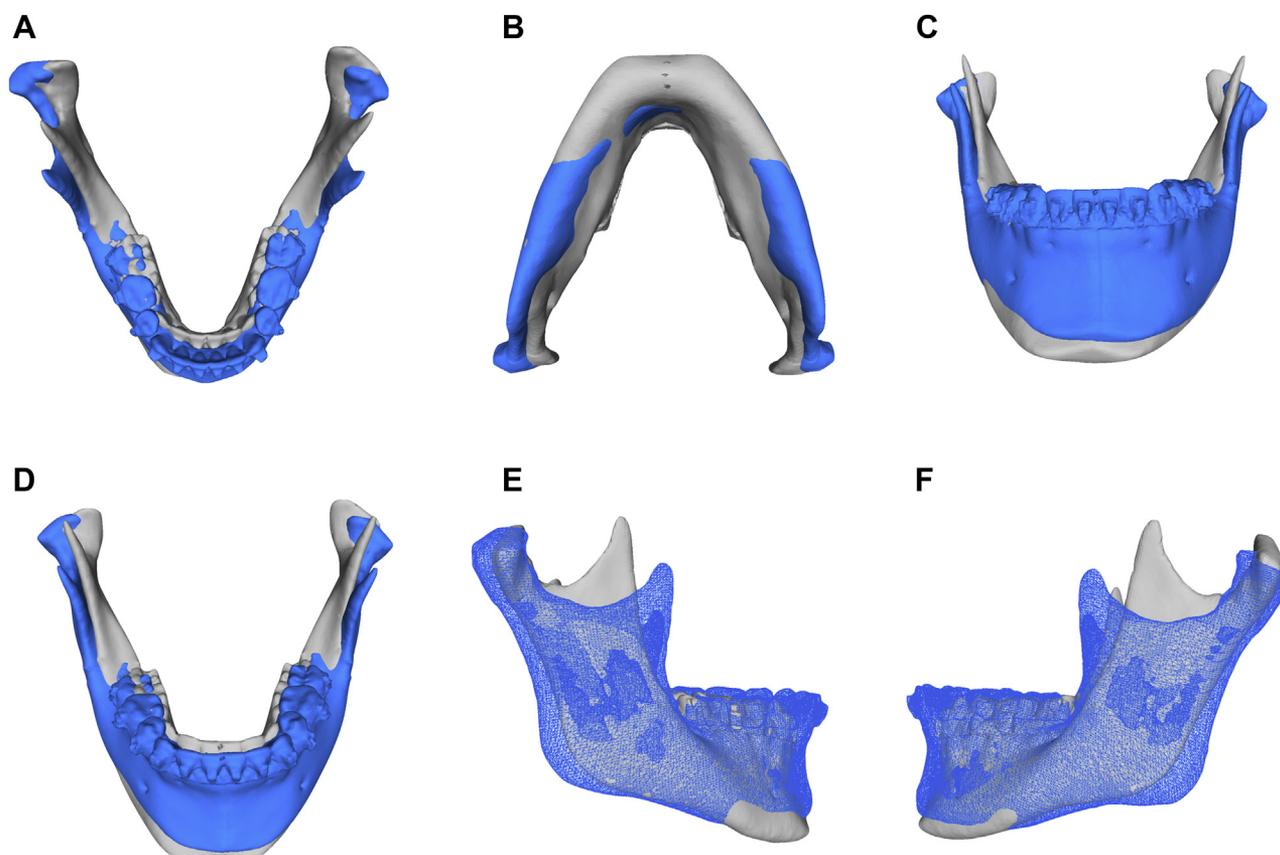
FIGURE 3. Shape changes represented in principal component 1. Asymmetric mandibles, at the positive end of principal component 1, are depicted in *gray* and mandibles at the negative end are depicted in *blue*. Note the main differences of the length of the left ramus.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

asymmetric mandible also was transversally compressed distally to the posterior teeth, with the condyle processes closer to each other. The rami were slenderer, with the coronoid process more vertically extended and oriented. The condyle of the left side was elongated, and the gonial angle was markedly more open. The body of the asymmetric mandibles was flattened on the affected side. This is visualized in Figure 3, which shows a superimposition based on the centroid of the extreme ends of PC1.

In contrast, PC2 (13.51%) and PC3 (8.22%) showed a large superimposition of groups (Fig 2), with features that were shared by cases and controls. The same occurred with subsequent PCs; hence, they are not presented. In other words, from PC2 onward, general trends of variation that were independent of the presence of CH-related asymmetry were found. The most remarkable features found in these PCs were divergence of the mandibular rami (Fig 4A, B, D), vertical extension of the condyles (Fig 4F), vertical (Fig 4E, F) and anteroposterior (Fig 5C-F) extensions of the chin, the aperture of the gonial angle (Fig 4E, F), and the overall robustness of the mandibles (Fig 5).

The difference in mean shapes of the 2 groups was statistically significant (Procrustes distance, 0.05; $P < .001$), despite the large number of features shared between groups. The latter was evidenced in the cross-validation, in which, based on their shape alone, 6 asymmetric mandibles (20%) could be classified as control mandibles and 4 control mandibles (13.33%) could be classified as asymmetric mandibles.

For size, asymmetric mandibles in men and women exhibited a larger centroid compared with controls. Differences were statistically significant among groups (H = 32.86; $P < .001$), but only men differed significantly from one another (Table 4). The effect of size on shape variation also was significant (variation predicted, 9.17%; $P < .001$; Fig 6), indicating that larger mandibles (asymmetric) exhibited different shapes than smaller mandibles (controls). This supports the idea of a strong connection between the size reached by the mandible and its geometry and degree of asymmetry.

Among landmarks, those corresponding to the left ramus and body (condyle head and mandibular border 1, respectively) were those that deviated most from
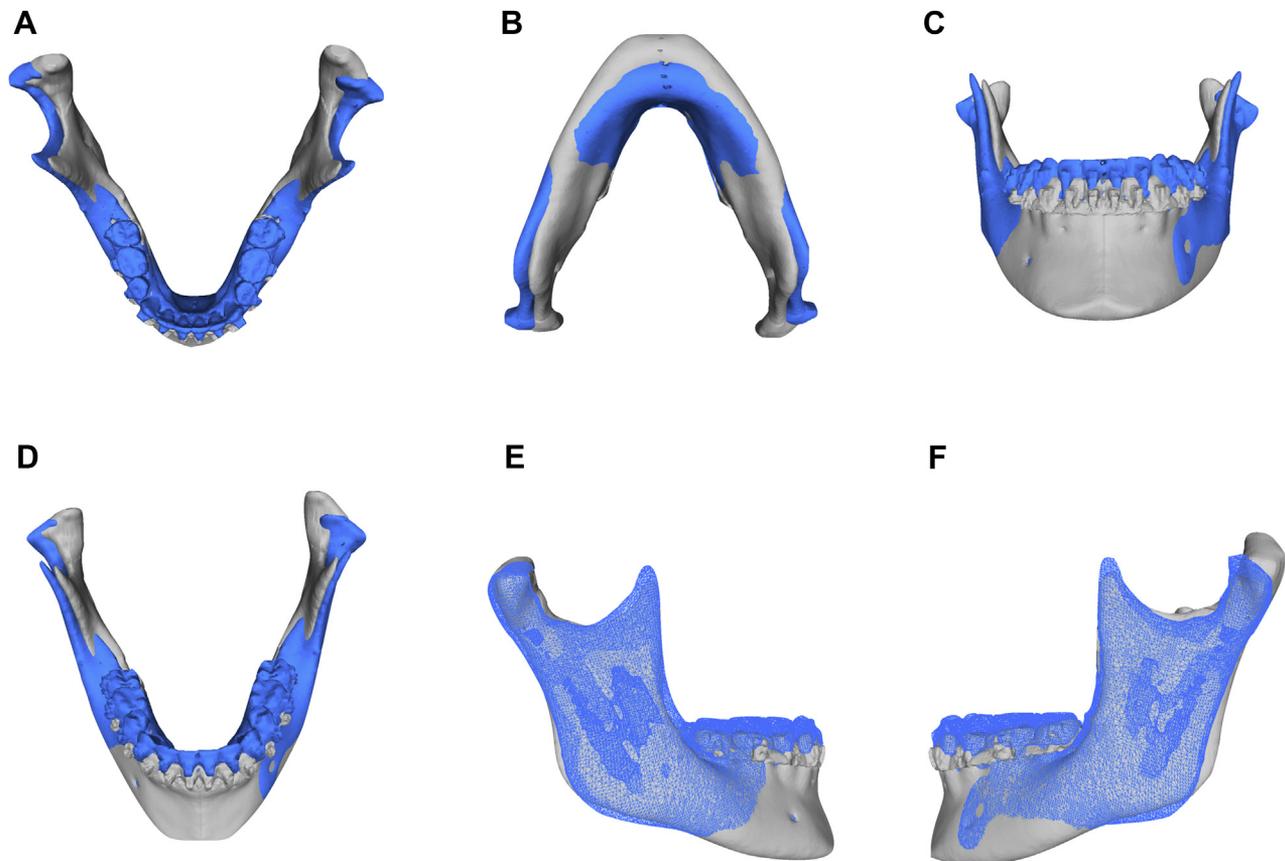
FIGURE 4. Shape changes represented in principal component 2. Features at the positive end of principal component 2 are depicted in *gray* and mandibles at the negative end are depicted in *blue*.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

their corresponding position for the control mean shape (Fig 7).

Discussion

This retrospective study compared the morphologic features between asymmetric CH-affected mandibles and control mandibles. Therefore, the aim of this work was to assess, in a virtual 3D environment, how and to which extent shape deformation occurs in asymmetric mandibles because of CH.

The inclusion criteria used for each group were defined by the threshold of a 4-mm deviation of the Me from the midfacial plane.[15,32,33] For this, a midsagittal craniofacial plane was established based on a reference midfacial plane composed of the nasion, basion, and incisive foramen.[34] However, in strict terms, the entire sample was asymmetric, given their distribution in the morphometric space (Fig 2). In relation to this, Gateño et al[35] measured the mean fluctuating asymmetry of the average-size face. In their sample, the results ranged from 1.0 to 2.8 mm (upper limit, 2.2 to 5.7 mm). Interestingly, the upper limit of asymmetry for the Me in their study was 3.3 mm, which is close to the value defined in the present study

for discriminating between symmetric and asymmetric mandibles.

One of the strengths of the present work is the use of GM analysis, a strong analytical tool for the study of 3D shapes that allows not only the detection (and visualization) of 3D shape changes but also their hierarchy according to the importance they have in differentiating groups. GM analysis is a multivariate statistical tool that has been used for decades in morphologic analyses of the human skull.[29-31] Despite its advantages and being a statistically sound technique, it has been used far less in dentistry, with orthodontics leading its use.[36-38] One of its advantages is the possibility to visualize, describe, and make functional interpretations of shape changes related to the studied condition or pathology. With this approach, it was possible to observe (compared with control mandibles) that asymmetric mandibles had greater divergence of the 2 rami, a flat contour of the affected body side (and a convex contour on the nonaffected side; Fig 3), and a larger whole structure. These features explain almost 23% of the total observed variance.

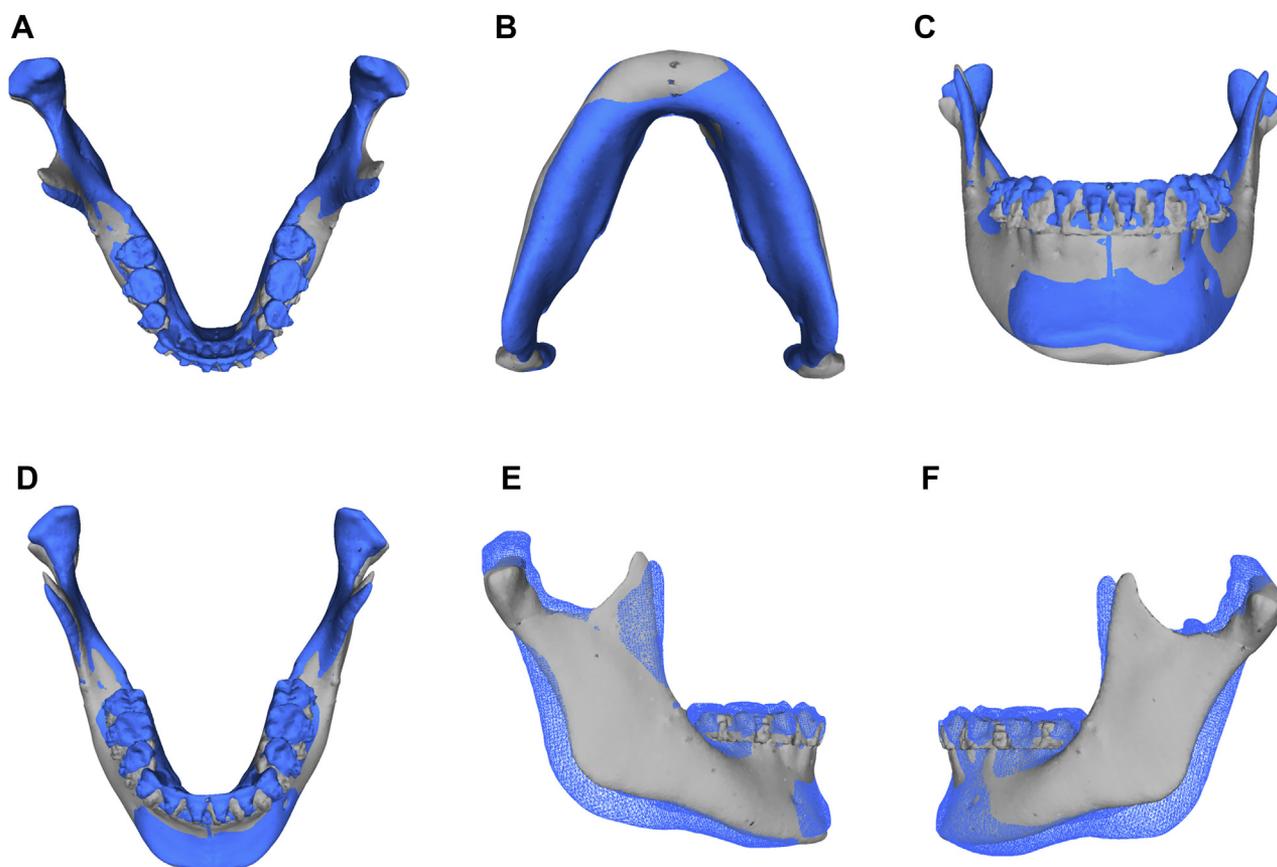The present results suggest that there are 2 main areas defining mandibular asymmetries associated

FIGURE 5. Shape changes represented in principal component 3. Features at the positive end of principal component 3 are depicted in *gray* and mandibles at the negative end are depicted in *blue*.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

with CH: the ramus and the mandibular body. The length of the ramus of the affected side is the feature that contributes most to the asymmetry. Maeda et al[39] evaluated participants with asymmetric mandibles through CBCT and observed that the ramus and the body are jointly involved in mandibular asymmetries. They added that, in extreme cases, the ramus would be primarily responsible. In contrast, Park et al[16] suggested (by performing a vector analysis on asymmetric mandibles) that the vertical growth of the mandibular condyle might not be the major structure responsible for chin deviation and mandibular asymmetry. They also considered that the symphysis was not important to mandibular asymmetry. This is interesting because, clinically, the chin seems to be an area that contributes most to asymmetry. Although some alteration of the chin was observed in the present study, it contributed to a lesser degree to the

Table 4. MANN-WHITNEY PAIRWISE TEST OF DIFFERENCES IN CENTROID SIZE (MEDIAN PER GROUP)

	Asymmetric Women	Asymmetric Men	Control Women	Control Men
Asymmetric women (277.89 mm)		4	106	64
Asymmetric men (302.82 mm)	<.001*		0	7
Control women (269.81 mm)	.03	<.001*		25
Control men (283.42 mm)	.03	<.001*	<.001*	

Note: Men and women were considered separately. The upper diagonal presents *U* values and the lower diagonal presents *P* values.

 * *P* values that remained statistically significant after Bonferroni correction.

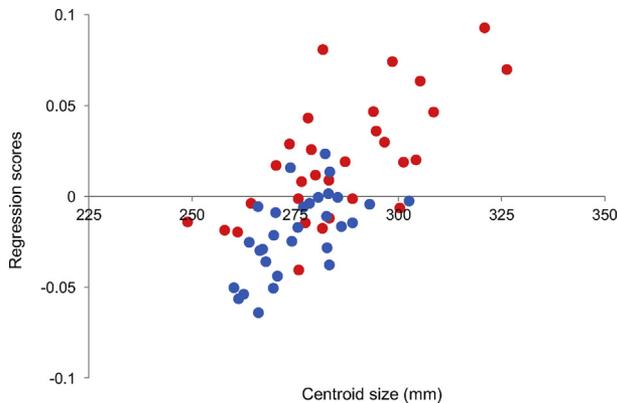*Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.*

FIGURE 6. Allometry analysis. Regression of shape variables (*vertical axis*) against centroid size. More asymmetric mandibles (*red*) tend to be larger than control mandibles (*blue*).

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

and body segments for linear and volumetric measurements, with the condyle being the most relatively affected area. The chin was not mentioned.

Although a structural chin deviation was noticeable in the present findings, relatively speaking, it did not seem to be particularly affected from the morphologic point of view (Figs 3, 7). Its vertical features were shared by the 2 groups (Figs 4, 5). Moreover, its landmarks were less deviated from the control mean mandibular shape (Fig 7). Interestingly, the midline landmarks on the chin and mental foramen on the right and left sides contributed less to the asymmetries. Therefore, it is worth asking how precise current parameters are in determining the diagnosis of CH-affected asymmetry without defining an accurate plane of symmetry. The symmetry plane is key for the diagnosis of the asymmetry, which can differ based on the method used to define this plane.[41] Because the method of alignment in this study was Procrustes analysis, a reference frame was not necessary to compare the morphometric characteristics between groups, so the results obtained were mainly related to structural features. Baek et al[15] investigated the skeletodental factors affecting chin point deviation in female patients with asymmetry. Although they did not describe the study group as patients with CH, they suggested that a mesial inclination of the ramus on the affected side and a shorter ramus height on the deviated side might be connected with the shift and rotation of the lower part of the mandible into the deviated side of the asymmetric group. Based on this, they attributed the deviation of the chin to the rami. This is in accordance with the present results, because the length of the ramus was the main feature affected in asymmetric mandibles in the present sample. As
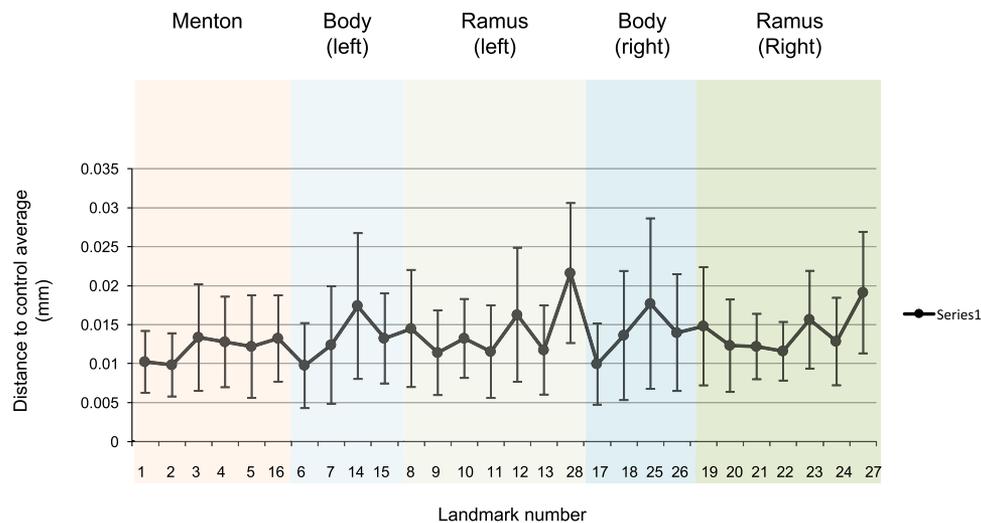
mandibular asymmetry than the mandibular structures mentioned earlier. This is especially important because only 1 of the 30 asymmetric mandibles in the CH sample could be classified as having a vertical growth pattern (HH), making the conclusions more valuable. Based on this, it is difficult to propose definitive statistical conclusions on the specific characteristics found in HH using GM analysis, because the most common type of asymmetry observed was HE. This could be explained by the finding that HH has a lower incidence than HE.[40] Nolte et al[18] quantified mandibular asymmetry in unilateral condylar hyperplasia with linear and volumetric measurements in asymmetric and control groups. Meaningful differences between the affected and unaffected sides in the patient group were found in the condylar, ramus,

FIGURE 7. Plot of landmark distances to the mean control shape. The contribution of each landmark to the shape changes in asymmetric mandibles is expressed as linear distances (mean and standard deviation) of each Procrustes coordinate to the mean control shape.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

mentioned earlier, the current diagnosis of CH-related asymmetry seems to depend on the plane of symmetry used (and the consecutive reference frame chosen) rather than being a structural property of the mandible. Indeed, there was a 20% misclassification of asymmetric mandibles (and 13.33% of controls). The position and orientation of the mandible relative to a craniofacial reference play important roles in the clinical expression of asymmetry. Hence, the treatment plan should be based on the symmetry plane defined for each case more than proposing it based on a specific classification or pattern of growth. In that way, a "customized" analysis of the mandible can be performed and residual asymmetries can be avoided. Many studies have assessed symmetry planes using different anatomic landmarks (all of them only in hard tissues).[34,41-44] In this study, the authors chose one that could be constructed on a daily basis in clinical practice with adequate methodologic quality in its assesment.[34] Further studies should be performed using GM analysis[45] or other mathematical methods[46,47] to evaluate the most reliable symmetry plane for routine clinical use.[44]

For age, it should be noted that part of the sample was composed of young patients in active growth (control group, n = 3; study group, n = 4). These patients represent 11.6% of the sample. Although this is a small proportion of the total sample, it could explain in part the large shape variation (and overlap) of the 2 groups. Conversely, and based on results of the allometry test, older full-grown adults showed more marked asymmetric features, contributing to the increase of differences between groups (Figs 2, 6). Either way, the general interpretation of the results remains unchanged.

From a biomechanical perspective, it is important to point out that a vertically extended symphysis offers less resistance to the shearing forces that act on it during unilateral clenching.[48] Considering the importance of mechanical loading in shaping bone,[49] it would be interesting to investigate whether the vertical extension of the mandible in these individuals corresponds to a mechanical necessity of increasing the resistance to another set of force vectors present in asymmetric mandibles (especially considering their increased biting lever arm owing to a shorter distance to the temporomandibular joint; Fig 3E, F) or simply to a weaker force during unilateral clenching, making the remodeling to a less circular symphysis unnecessary.

Surgical management of CH-related asymmetries can be accomplished through condilectomy[50-53] orthognathic surgery,[54] or their combination.[55-57] In any of these procedures, correction of the asymmetry is based mainly on correction of the mandibular position in relation to the chosen facial symmetry plane (hence, the mandible's yaw, pitch, and roll

orientation are changed). However, sometimes correcting these elements is not enough because of the presence of residual asymmetries within the mandible,[33] as seen in the present results. Condylectomy has been proposed as a sole treatment,[51,58] in which progressive growth is stopped and asymmetry can be corrected in a successful manner. Considering that the most affected area is the ramus, it makes sense that many times a condylectomy is sufficient.[58] An exception to this would be HH, in which the main asymmetry is due to a vertical pattern of growth of all parts of one side of the mandible. In HH cases, further osteotomies might be required to correct the asymmetry because the chin is usually not compromised.[40,59] Thus, because of the complex combination of features seen in mandibular asymmetries,[60] residual asymmetries can still be found after a condylectomy or orthognathic surgery.[33] This could be related to the other, less described features found in the present sample, such as a flattened body on the affected side and convexity on the nonaffected side. These features are difficult to measure and correct during CASS.

All these findings lead to deeper questions on the therapeutic approaches in CH-related asymmetry, considering all the structures that are affected. Thus, it is worth asking whether treatment planning based on mirror-imaging analysis should be reconsidered to favor more integral analysis of the mandible in the way that GM analysis does.

It has been reported that CH affects more women than men,[13] as confirmed in the present sample. Raijmakers et al[61] proposed female gender as a risk factor for CH in a meta-analysis. However, the present results
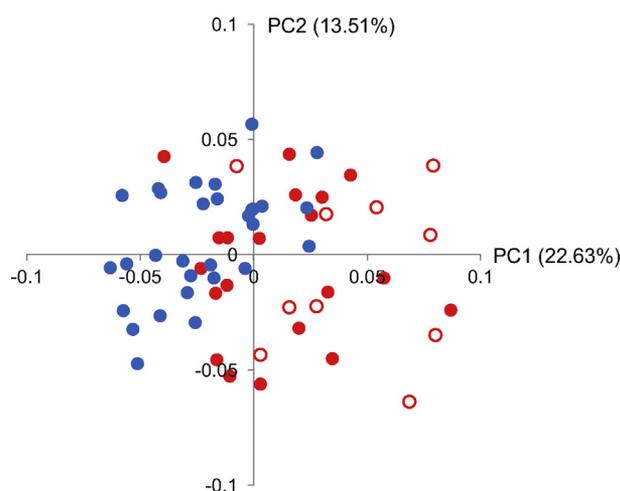

FIGURE 8. Gender contribution to shape changes depicted by PC1. Asymmetric men (*open red circles*) tend to show more extreme asymmetric features than asymmetric women (*solid red circles*) and the entire control group (*blue circles*). PC1, principal component 1; PC2, principal component 2.

Espinosa, Rabanal, and Toro-Ibacache. Mandibular Asymmetry and Condylar Hyperactivity. J Oral Maxillofac Surg 2019.

suggest that its morphologic effect could be more striking in men than in women, because the more marked features describing asymmetric cases are mostly held by men (open red circles in Fig 8). This could be related to the longer growth period in men,[62,63] which makes them reach a larger size. This larger size in patients with CH is associated with a comparatively more altered shape, as the allometry test indicates (Fig 6).

The null hypothesis is rejected, because there are marked differences between symmetric and CH-related asymmetric mandibles in the areas described earlier. All mandibles had structural asymmetry, likely because of intrinsic and developmental instability (causing directional and fluctuating asymmetry, respectively). However, there are structures that show marked degrees of variations that eventually are responsible for the clinical features found in patients with CH.

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