Morphologic variability of nonsyndromic operated patients affected by cleft lip and palate: A geometric morphometric study

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Introduction: In this study, we compared patterns of morphologic variations of the craniofacial skeleton between patients affected by clefts who were operated on and unaffected subjects, aiming to discuss possible morphofunctional consequences of treatment in craniofacial development. **Methods:** The lateral cephalograms of 76 subjects, comprising patients with operated unilateral cleft lip and palate (OpC) and a group matched for sex and age without cleft, were used. Thirteen landmarks were used as variables in geometric morphometric tests quantifying and describing overall shape variation, differences between group means, allometry, and upper-lower face covariation. **Results:** The OpC group showed broader shape variations including noncleft group characteristics, but mainly a retrognathic maxilla, a vertically elongated face, a more open mandibular angle, and a more closed basicranial angle. Group means differed mainly in the maxillomandibular relationships. Allometry differed between groups, with the smallest OpC patients showing the most altered morphology. Upper and lower face covariation was stronger in the OpC group, showing mainly vertical changes in the anterior face. **Conclusions:** Operated patients affected by clefts achieve a broad range of morphologies; the most altered were found in those with skeletal Class III and small size. Furthermore, their strongest upper and lower face shape covariation suggests that a harmonic dental occlusion could be a key factor in achieving "normal" craniofacial morphology. (Am J Orthod Dentofacial Orthop 2014;146:346-54)

Clefts of the lip and palate (CLP) are common congenital anomalies. The incidence is highly variable among populations. The highest incidence is found in Asians and Native Americans, with 1 in 500 live births, and the lowest in Africans, with 1 in 2500 births; white, Hispanic, and Latin populations (among these, Chileans) have intermediate incidence of 1 in 1000 live births.[1-4] Cleft etiology is multifactorial, comprising both genetic and environmental factors acting during intrauterine development.[5-7]

Unilateral CLP (UCLP) is the most common cleft type.[5,8] Morphologic alterations of operated patients with UCLP have been widely reported in the literature, of which changes in maxillomandibular relationship are the most prevalent, as described below. Since unoperated subjects have the potential to develop a "normal" (ie, skeletal Class I) maxillomandibular relationship,[9,10] it has been proposed that altered maxillomandibular relationships are caused by the effect of surgery, particularly lip closure, on the developing bone and sutures.[11-13] This has led to the proposal of different protocols for the surgical management of CLP that concur in the importance of reconstructing the muscular anatomy of the lip and the soft palate after the third month of age.[12,14-16]

Despite the differences in surgical approaches and treatment protocols, the morphologic features in operated patients with UCLP tend to be uniform. In general,

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they are described as having a retrognathic maxilla.[11,12,16] They also show asymmetric faces[17] and altered growth of the transversal[18,19] and vertical[19-21] facial dimensions. Alterations of the cranial base have also been reported, although authors do not agree about these descriptions.[19,20]

Among the methods used to describe and compare skull morphology in individuals affected by orofacial clefts, the use of linear morphometrics and univariate statistics is common. These have some limitations related to the difficulty in assessing separately the changes in shape and size and the impossibility of capturing the geometry of all the areas of interest.[22] The advances in multivariate statistics and computer technology over recent decades have led to the development of geometric morphometrics, a statistical tool widely used for the quantitative study of the shape (ie, form minus size) of organisms. Geometric morphometrics also allows visualizing the changes in morphology associated with the variables of interest.[22-24] This statistical tool has been applied in studies of operated individuals affected by cleft to characterize their face surface[17,25] and that of their parents.[26] Geometric morphometrics has also been used to study cranial morphology in affected individuals in the frontal plane[21] and the anteroposterior changes in shape during growth.[27] It has been used in mice to assess developmental integration in the skull of cleft-susceptible mouse strains.[28]

We used geometric morphometrics analyses in this study to compare the craniofacial morphologies of a group of operated patients with UCLP with a control group of unaffected subjects with normal occlusion. We tested the general null hypothesis that patients with operated UCLP and unaffected subjects show the same patterns of craniofacial shape variations. Four parameters were studied: general shape variations, differences in mean shape between groups, allometry, and shape covariation between the upper and lower face.

MATERIAL AND METHODS

Ethical approval was granted from the Scientific Ethical Committee of the Faculty of Dentistry, University of Chile (number 2013/34) for the use of image data from the faculty's clinical records.

The sample comprised the lateral radiographs of 76 persons: 38 (19 men, 19 women) patients with nonsyndromic, operated UCLP (OpC group); and 38 (19 men, 19 women) control subjects with Class I dental occlusion and with an overall harmonious skeletal and soft-tissue profile (NonC group). All the radiographs belonged to patients from the dental clinic of the University of Chile and were taken for medical reasons (diagnosis or treatment evaluation) before the beginning of this study. The radiographs had been taken according to the institutional protocol at the time, with pano/ceph equipment (Siemens Healthcare, Erlangen Germany) operated at 75 to 80 kV and 20 to 25 mA. The position of the head was determined by the cephalostat, fixing the position of the external acoustic meatus and nasion.

All patients were Chileans living in Santiago de Chile or the surrounding areas, representing a dihybrid sample of Amerindian-Spanish admixture with varying levels of the Amerindian component. Those with a greater Amerindian component have been associated with a higher susceptibility to clefts compared with subpopulations of white origins.[29] The mean ages were 13.1 $\pm$ 2.67 years in the OpC group and 12.68 $\pm$ 2.28 years in the NonC group. Patients in the OpC group had undergone cosmetic surgery of the soft tissues and orthodontic treatment without orthognathic surgery or orthopedic treatment with a maxillary-traction facial mask. The primary cleft closure of the patients in the OpC group was performed at a few clinical institutions by various surgeons in Chile. When these patients were operated on, most surgeons in Chile used an approach based on the Tennison-Randall, Skoog, and Millard techniques, with the primary lip closure performed at 3 months of age, the primary soft-palate closure at 12 months, and the hard-palate closure performed simultaneously at one of these times.[30]

The 2-dimensional geometry of the cranial base, upper face, and mandible was captured using 13 landmarks (Table I, Fig 1). They were selected according to the criteria of Bookstein[31] and Dryden and Mardia[32] for biologic landmark data. To improve the comparability with other studies in the field, most of the selected landmarks were based on those of Delaire et al.[33] The number of landmarks used was considered sufficient to capture key anatomic features and appropriate to increase the statistical power of analyses (see the studies of Bookstein[34] and Monteiro et al[35] for recommendations about the optimal number of landmarks and sample size). The landmarks were marked by 1 observer (A.D.M.) on a transparent acetate sheet placed on each radiograph and revised by a second observer (J.C.A.). Raw data in the format of x and y coordinates representing each landmark were digitized by 1 observer (V.T.-I.) using a mechanical digitizing system (MicroScribe; Immersion, Palo Alto, Calif). Landmark coordinates were exported as text files to be used in subsequent analyses. To assess the effect of measurement error, 16 subjects (4 men and 4 women from each of the 2 groups) were redigitized on 6 different days.

Statistical analysis

The geometric morphometric analyses were performed on shape variables. These were obtained by Procrustes fit, which consists of translation, rotation, and