Longitudinal Craniofacial Growth Patterns in Patients With Orofacial Clefts: Geometric Morphometrics

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Objective: **To demonstrate craniofacial developmental patterns in repaired cleft lip and cleft palate (CLP).**

Design: **Retrospective, longitudinal.**

Setting: **Center for Craniofacial Disorders, San Juan, Puerto Rico.**

Sample: **Males aged 9 to 17 years: 13 noncleft (NC) Class I occlusion (NCC1); 13 NC Class III malocclusion (NCC3); 12 CLP Class I occlusion (CLPC1); and 15 CLP Class III malocclusion (CLPC3).**

Main Outcome Measures: **Form changes (ages 10, 13, and 16 years), using finite-element scaling analysis.**

Results: **NCC1, 10 to 13 interval: 30% size increase in upper midface ($p < .05$), mental region ($p < .01$), mandibular body ($p < .05$); 13 to 16 interval: 10% to 35% size increase in bimaxillary region and ramus ($p < .01$). NCC3, 10 to 13 interval: 10% to 40% size increase in posterior cranial base, upper midface, and mandible ($p < .05$); 13 to 16 interval: 10% to 30% size increase in bimaxillary region ($p < .01$), especially ramus. CLPC1, 10 to 13 interval: 10% to 15% size increase in posterior cranial base ($p < .01$), midface ($p < .05$), and mandibular ramus ($p < .05$); 13 to 16 interval: 8% to 20% size increase in upper midface ($p < .01$), lower midface ($p < .05$), and mandible ($p < .05$). CLPC3, 10 to 13 interval: no significant changes; 13 to 16 interval: upper midface and cranial base show nonsignificant size decreases, but ramus showed size increase.**

Conclusions: **Noncleft and CLP Class 1 occlusion groups show similar craniofacial growth patterns. Noncleft Class III groups show excessive cranial and mandibular growth. Class III malocclusion in CLP patients is associated with clinically deficient craniomaxillary growth. Growth guidance may be indicated in children with CLP with unfavorable craniofacial growth patterns.**

KEY WORDS: *cleft lip palate, development, geometric morphometrics, growth guidance*

Rehabilitation of the patient with cleft lip and palate (CLP) must be based on a thorough knowledge of their growth potential, because even after surgery the patients' tissue development often does not follow usual growth trajectories. Anomalous growth of the midfacial area after corrective surgery may be associated with several complications such as unclear patterns of speech, velopharyngeal deficiencies, skeletal deformities, and dental malformations, which contribute to facial disfigurement and low self-esteem. Thus, postsurgical results are not always predictable because the response of growing tissues to surgical repair is variable, leading to phenomena such as midfacial hypoplasia (Graber, 1949; Kim, 1958; Subtelny, 1962; Levin, 1963; Dahl, 1970; Krogman, 1975; Horowitz et al., 1976; Ross, 1965). To overcome problems that often occur during postsurgical development, patients may require additional surgical procedures, but the behavior of growing tissues is one factor that needs to be addressed to prevent less successful outcomes.

In the analysis of clinical data, cephalometry has been employed extensively, and some believe that manual superimposition is valid (Schudy, 1996). However, the results of cephalometric analyses can show remarkable differences (Hurmerinta et al., 1997) and may even generate controversy (Anderson and Popovich, 1983). Nevertheless, quantitative study of

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form and form change comprises the emerging field of geometric morphometrics, which provides more detailed descriptions of observable clinical changes (McAlarney and Chiu, 1997). These newer techniques include thin-plate spline analysis (e.g., Pae et al., 1997; Singh et al., 2003), Euclidean distance matrix analysis (EDMA; Lele and Richtsmeier, 1991, 1995; Hay et al., 2000), and finite-element scaling analysis (FESA; Richtsmeier, 1987; Cheverud et al., 1991; Richtsmeier and Lele, 1990; Singh and Clark, 2003). Thus, to assess postsurgical changes, quantitative analysis of form may be based on the use of landmark coordinate data. For example, using FESA, Hammond et al. (1993) reported that the cranial base is unaltered in unilateral cleft lip and palate.

The overall aim of this study was to determine craniofacial developmental patterns in four groups of patients: two groups with repaired CLP and two similar noncleft (NC) groups, using FESA to model craniofacial growth. These comparisons will help to identify skeletal tissue differences because these differences might be associated with growth consequences. Therefore, this study attempted to localize and quantify craniofacial differences in boys to elucidate facial development patterns, which might aid clinicians in the formulation of treatment plans to optimize facial growth postsurgically. The null hypothesis to be tested was that the craniofacial development in NC subjects is not significantly different from that of patients treated for CLP. Rejection of the null hypothesis may indicate whether facial growth guidance might be used to simulate normal facial development.

Materials and Methods

Sample and Landmark Data

In this retrospective, longitudinal study, the sample consisted of a total of 53 white males aged 9 to 17 years. Angle sella-nasion-point A (SNA) was used to classify individuals into groups to be studied. Class I was considered to present an average maxillary position (angle SNA of 86 to 88 degrees), whereas Class III represented relative maxillary retrusion (angle SNA of 75 degrees or less).

Typical orthodontic classification schemes using the cuspid or molar classification were not considered for the classification of the patients. Using this criteria, 13 individuals were NC subjects with a normal, Class I occlusion, designated group NCC1; 13 were NC subjects with Class III malocclusion (group NCC3); 12 were patients who had undergone primary surgical repair at about age 1 year for complete unilateral cleft lip and palate, showing normal, Class I occlusion, designated group CLPC1; and 15 were patients who had undergone primary surgical repair for complete unilateral cleft lip and palate, showing Class III malocclusion (group CLPC3). Each of the four subsamples was organized into three age groups, as shown in Table 1.

No preoperative patients were included in this study, but all patients had undergone conventional fixed appliance orthodontic treatment but not orthopedic or surgical correction. Exclusion criteria for the patients without cleft included being a sibling of a patient with a cleft, whereas for the cleft patients, it included the presence of a velopharyngeal flap either prior to or during the study period. Therefore, the groups were comparable on the basis of race, sex, age, class of occlusion, and cleft condition.

TABLE 1 Organization of Four Subject Groups Into Three Age Groups

*Subject Group**	*Age Group*		
	T1	*T2*	*T3*
NCC1	10.33 ± 0.67	12.92 ± 0.83	15.67 ± 0.50
NCC3	10.50 ± 0.42	13.17 ± 0.67	16.60 ± 1.00
CLPCI	10.08 ± 0.58	12.58 ± 0.75	15.75 ± 1.08
CLPC3	10.16 ± 0.33	13.00 ± 0.83	16.33 ± 1.00

* NCC1 = subjects without cleft with normal, Class I occlusion; NCC3 = subjects without cleft with Class III malocclusion; CLPCI = subjects treated for complete unilateral cleft lip and palate with normal, Class I occlusion; CLPC3 = subjects treated for complete unilateral cleft lip and palate with Class III malocclusion.

From the lateral cephalographs, eight skeletal landmarks were identified (Figure 1) and digitized using appropriate software to obtain their x, y coordinates. All data were subjected to duplicate digitization. Next, Procrustes superimposition was implemented to obtain a generalized rotational fit (Rohlf and Slice, 1990). That is, all configurations were scaled to an equivalent size and registered with respect to one another (Singh et al., 1997c). Thus, the mean craniofacial morphologies were determined for all groups at the three ages to be tested, and a perturbation model (Rohlf and Slice, 1990) was used to compare the mean NC and mean cleft group morphologies during two time intervals (i.e., T1 versus T2 and T2 versus T3).

To demonstrate sources of heterogeneic developmental morphogenesis, a FESA was undertaken that incorporated a spline interpolation function (Bookstein, 1991). A FESA can be used to depict developmental transformations in terms of allometry (size-related shape change) and anisotropy (directionality of shape change). Based on this approach, differences can be described graphically as a size-change, shape-change, or both (e.g., Singh et al., 1997a, 1997b). New FESA software (MorphoStudio, www.orthovisage.com) was written in C++ and implemented on a personal computer. Change in form between the reference configuration and the final configuration is viewed as a continuous deformation, which can be quantified based on major and minor strains (principal strains). If the two strains are equal, the form change is characterized by a simple increase or decrease in size (Lozanoff, 1990). However, if one of the principal strains changes in a greater proportion, the transformation occurs in both size and shape. The product of the strains indicates a change in size if the result is not equal to 1. A product greater than 1 represents an increase in size equal to the remainder; for example, 1.30 indicates a 30% increase. On the other hand, a result of 0.80 indicates a 20% decrease in size.

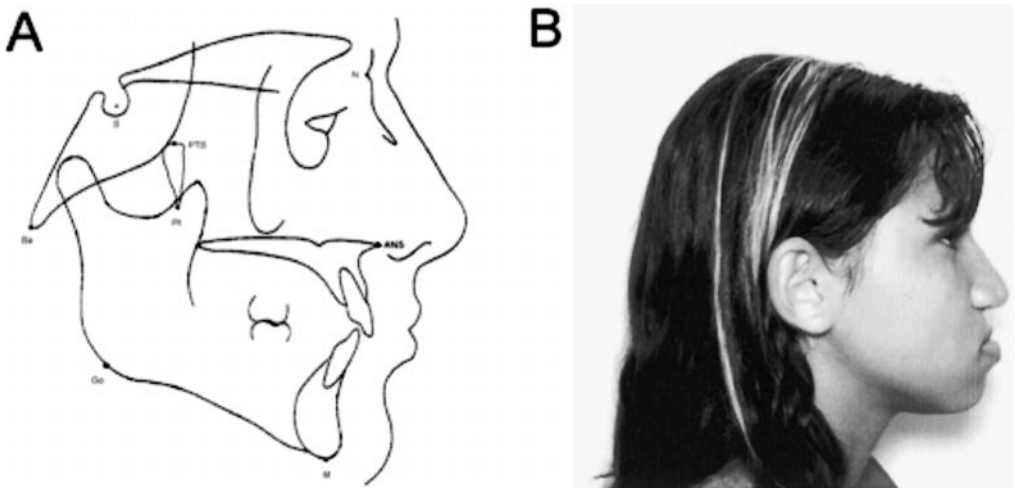

FIGURE 1 A: Definitions of landmarks employed in this study. ANS = anterior nasal spine, anterior-most point on anterior nasal spine; Ba = basion, lowest point on the anterior border of the foramen magnum; M = menton, inferior-most point on the mandibular symphysis; N = nasion, anterior-most point of the frontonasal suture; Pt = inferior pterygomaxillare, the most inferior point on the outline of pterygomaxillary fissure; PTS = superior pterygomaxillare, the most superior point on the outline the pterygomaxillary fissure; S = sella turcica, the center of the bony outline of sella turcica; Go = gonion, the midpoint at the angle of the mandible. B: Clinical illustration of a 10-year-old girl with repaired cleft lip and palate, showing a severe Class III appearance associated with apparent midfacial retrusion.

Changes in shape are determined by the ratio of the principal extensions, where a value not equal to 1 represents an observable change in shape. The products and ratios can be resolved for individual landmarks within the configuration, and these can be linearized using a log-linear scale and pseudocolor coded to provide a graphic display of size- and shape-change (Lozanoff, 1990). For statistical testing, the Procrustes means were rescaled to their original dimensions and Student's *t* tests applied to identify elements showing significant changes.

Results

For corresponding craniofacial configurations, comparing T1 versus T2 and T2 versus T3 growth intervals (Figs. 2 through 5), the FESA results indicated that nearly all configurations (except the cleft Class III comparisons) showed areas of significant difference ($p < .05$).

Noncleft Class I Occlusion

The color-coded graphics produced by FESA (Fig. 2A and 2B) indicated regions in which size differences were evident. The 10- to 13-year-old NC growth interval showed approximately 15% increase in anterior and posterior cranial base size as well as similar increases in the upper and lower midface ($p < .01$) as well as in the mandibular body ($p < .05$). Animating these findings (using MorphoStudio software) indicated normative growth trajectories in the cranial base, midface, and mandibular regions.

Similarly, the 13- to 16-year-old NCC1 configuration indicated changes in the upper and lower midface ($p < .01$) as well as an approximately 35% increase in the mandibular ramus ($p< .01$) and body ($p < .05$), presumably representing the mandibular growth spurt at puberty (Fig. 2B).

Noncleft Class III Malocclusion

For the 10- to 13-year-old NC Class III patients, using FESA, the 10- to 13-year-old growth interval showed a 10% increase in size in the upper midface ($p < .05$) and an approximately 20% increase in size in the mandibular body and mental region ($p < .05$) in conjunction with a large increase localized in the posterior cranial base (Fig. 3A). However, for the 13- to 16-year-old NC Class III, FESA of the configuration (Fig. 3B) showed continued changes in the upper midface and lower midface ($p < .01$), with conspicuous development in mandibular body and ramus areas ($p < .01$).

Cleft Class I Occlusion

Using FESA for the 10- to 13-year interval (Fig. 4A), the color-coded configuration showed 15% to 20% size increase in the posterior cranial base ($p < .01$), midface ($p < .05$), and mandibular ramus ($p < .05$). The 13- to 16-year-old cleft Class I interval (Fig. 4B) showed 15% to 20% size increases in the upper midface ($p < .01$) and lower midface ($p < .05$), mandibular body, and ramus ($p < .05$). Animation indicated growth trajectories in the cranial base, midface, and mandibular regions similar to those found in the NC Class I groups.

Cleft Class III Malocclusion

For the 10- to 13-year interval using FESA, the comparison (Fig. 5A) showed a small size increase at Pt. In contrast, the

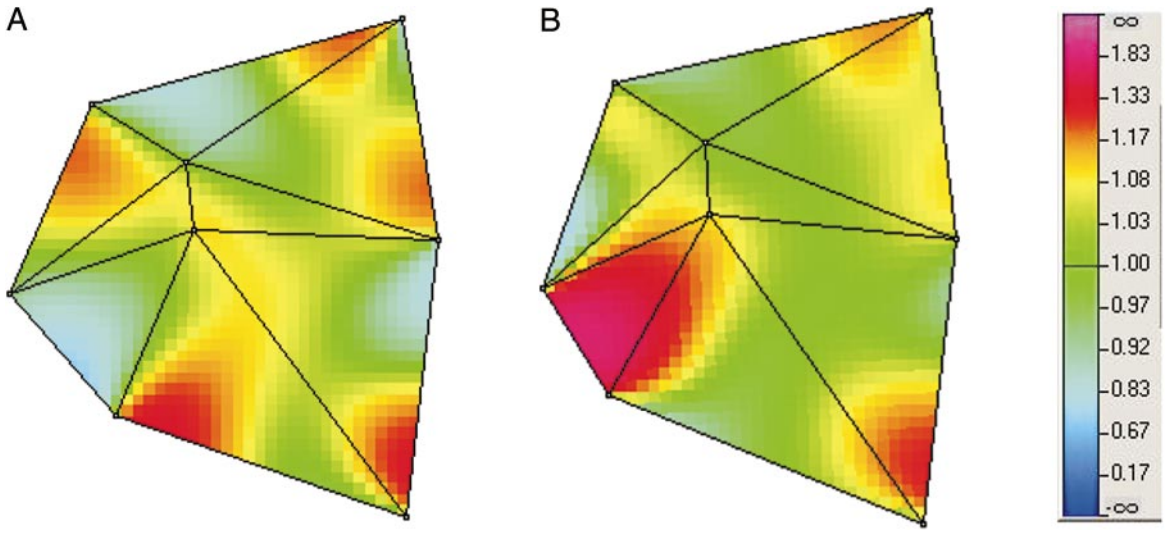

FIGURE 2 Noncleft Class I. A: The 10- to 13-year comparison shows an approximately 15% increase in anterior and posterior cranial base size, upper and lower midface, and mandibular body (red-yellow regions). B: A 13- to 16-year comparison, indicating changes in the upper and lower midface as well as an approximately 35% increase in the mandibular ramus and body, presumably representing the mandibular growth spurt at puberty.

cleft 13- to 16-year interval showed an approximately 60% decrease in size of the cranial base and midfacial areas, but a 30% increase in size of the mandible in the 13- to 16-year interval (Fig. 5B). Surprisingly perhaps, these findings failed to reach levels of statistical significance.

Taken together, the FESA findings indicate that Class III malocclusion in this particular group of non-cleft boys developed at the pre-pubertal stage and is associated with relatively excessive posterior cranial base and mandibular growth. In contrast, a similar Class III appearance in patients with repaired clefts appears post-puberty, associated with clinically deficient cranial and midfacial growth.

DISCUSSION

The nature of obtaining landmark coordinates from lateral cephalographs is difficult, and to quantify the reliability of the digitization, duplicate evaluation of the error was performed at two different times for each of the four groups. As expected, the error of measurement varied with the measure under scrutiny with a best case of 0.028 mm and an r value of 0.99, to a worst case of 1.01 mm with a correlation coefficient of 0.96. The combined correlation coefficient for all measurements was 0.95, indicating that a high level of reliability was obtained. Working under the constraints of parsimony, however, reduc-

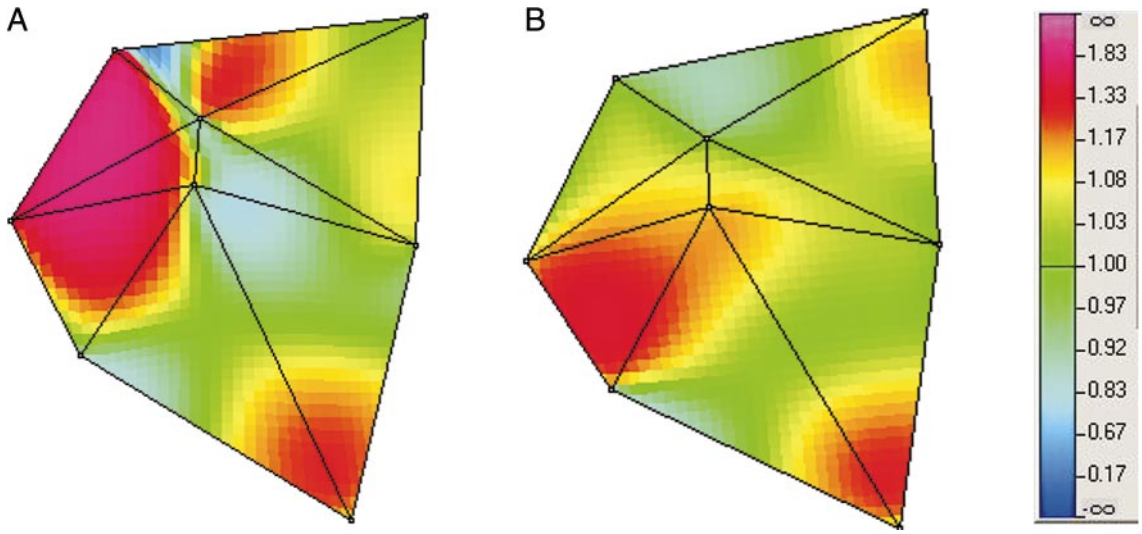

FIGURE 3 Noncleft Class III. A: The 10- to 13-year comparison shows a 10% increase in size in the upper midface (yellow) and an approximately 20% increase in size in the mandibular body and mental region (red) in conjunction with a large increase localized in the posterior cranial base (≈60%), presumably associated with the appearance of Class III malocclusion. B: A 13- to 16-year comparison shows continued changes in the upper midface and lower midface (yellow-red regions), with conspicuous development in mandibular body and ramus areas (red regions ≈35%), presumably representing the mandibular growth spurt at puberty.

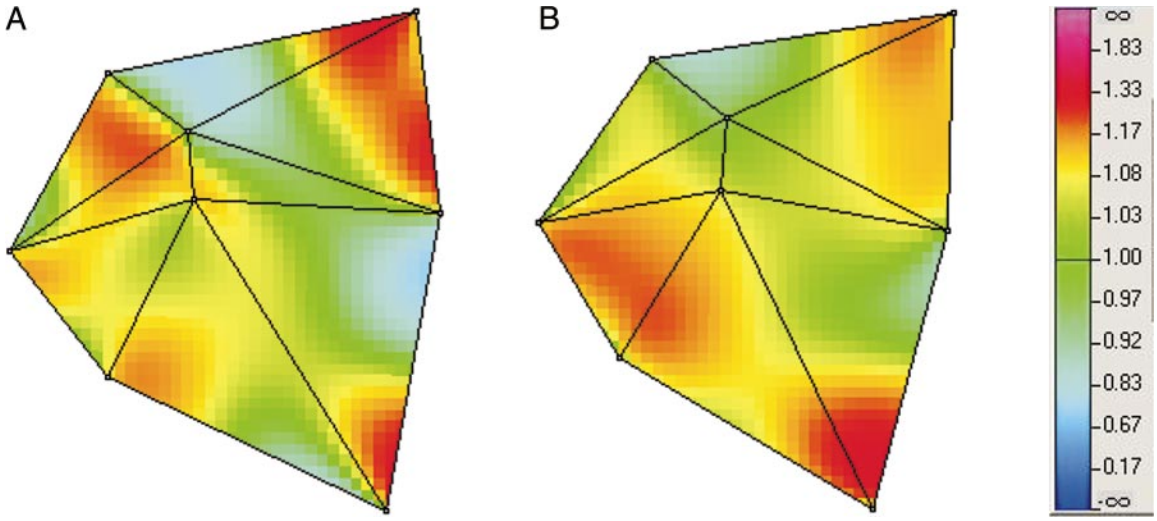

FIGURE 4 Cleft Class I. A: The 10- to 13-year comparison shows a 15% to 20% size increase in the cranial base (red-yellow), the midface (red), and the mandibular ramus (yellow). B: The 13- to 16-year comparison shows a 15% to 20% size increase in the upper midface (yellow-red) and lower midface (red), mandibular body, and ramus (yellow-red).

tion of a three-dimensional structure into a two-dimensional radiograph may lead to loss of crucial information. Nevertheless, statistical models may be used to represent intrapopulation variability of landmark data, even though it is acknowledged that arbitrary translation, rotation, and reflection of objects can introduce nuisance parameters (Mardia, 1999). Despite these limitations, the deployment of geometric morphometric techniques successfully analyzed the data available and provided some meaningful results.

The cranial base is an important developmental structure and the S-N line has been used as a reference plane for the assessment of the anterior cranial base (ACB) in craniofacial deformities (Sarhan, 1995). Indeed, Cohen et al. (1985) reported a shortened posterior cranial base and an acute cranial base angle in mandibular prognathism (Class III malocclusion) associated with achondroplasia. Later, Dolci et al. (1991) found a reduction in the length of the ACB in adults with mandibular prognathism. These findings are similar to the results of Singh et al. (1999a), which indicated that Korean children appear to develop Class III malocclusion because of smaller anterior cra-

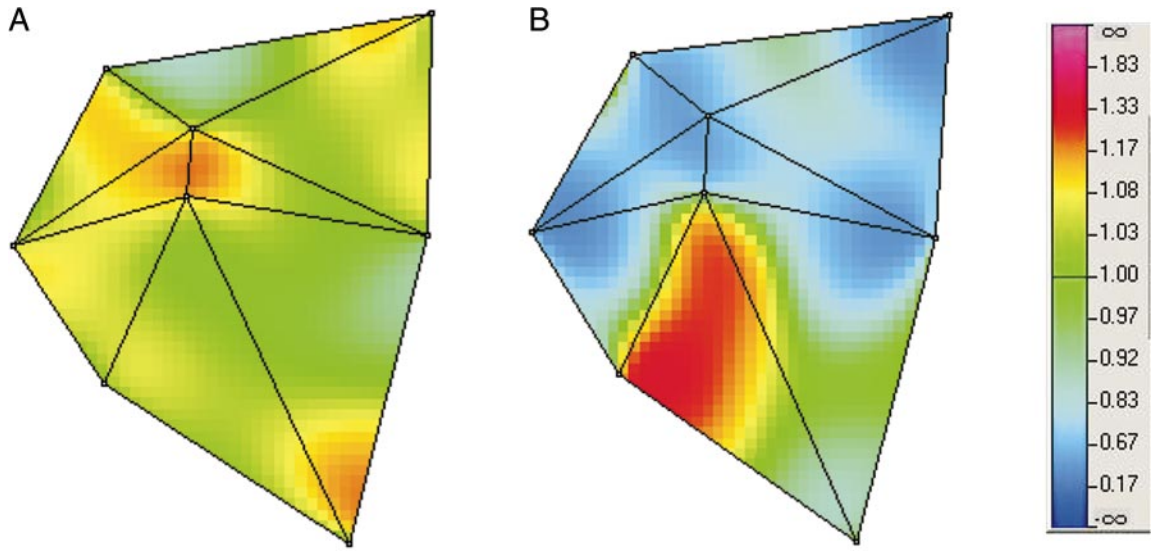

FIGURE 5 Cleft Class III. A: Note that although the 10- to 13-year comparison shows a few regions of size increase, this group demonstrates a Class III malocclusion clinically (see Fig. 1B). Thus, the spatial regions at ages 10 and 13 years have been largely maintained for this group. B: Note that deficiencies in size (≈30%) are localized in the anterior, middle, and posterior cranial base as well as the midface (blue areas). In contrast, the gonial region of the mandible shows an increase in size (≈30%), which presumably exacerbates the existing Class III condition, possibly requiring further surgical intervention for the relative midfacial retrusion. Surprisingly perhaps, these findings failed to reach levels of statistical significance.

nial base and midfacial consequences (Singh et al., 2000b), possibly because of premature synostosis at the sphenoethmoidal synchondrosis. Hamway and Pangrazio-Kulbersh (1995) suggest that normalization of ACB landmarks is important in ACB analysis, and this procedure was adopted as a part of this current study. Following this procedure, it was found that in NCC1 groups, the cranial base showed normative growth, whereas the NCC3 groups showed excessive posterior cranial base growth, presumably associated with temporospatial patterning at the spheno-occipital synchondrosis, which is related to the genome of the individual. Thus, these findings support the contention that Class III malocclusion is associated with cranial base morphology (e.g., Singh et al., 1997a, 1997c, 1999a). Using magnetic resonance imaging scans, Sgouros et al. (1999) found that most growth changes in the cranial base occurred normally before age 5 years. However, in this current study, deficiencies (≈30%) localized in the cranial base became apparent in the CLPC3 group during the 13- to 16-year interval. These findings support the suggestion that the cranial base provides an early genetic or developmental template for postnatal maxillomandibular growth (Martone et al., 1992) and that the final phenotypic outcome is liable to later environmental modulations, such as (surgical) trauma.

Friede and Morgan (1976) reported that traumatic surgery impairs midfacial growth, resulting in midfacial retrusion and a concave skeletal profile (Friede and Pruzansky, 1985; Fig. 1B). More recently, however, Padwa et al. (1999) suggested that surgical premaxillary repositioning can be undertaken without compromising subsequent facial growth, and Wood et al. (1997) were unable to distinguish impairment of skeletal maxillary growth in the absence or presence of gingivoperiosteoplasty. Nevertheless, distraction osteogenesis is still commonly required for maxillary midface advancement in children with midfacial hypoplasia associated with CLP (Polley and Figueroa, 1999), whereas Class III malocclusion may be treated using maxillary protraction, expansion, or both (Mermigos et al., 1990; Shanker et al., 1996; Williams et al., 1997; Baccetti et al., 1998). These studies suggest that the observed Class III profile might be associated with the underlying cranial base genotype (e.g., Singh et al., 1997a, 1997c, 1997d). In the present study, for the CLPC3 groups, deficient growth (≈30%) was localized in the midface as well as the cranial base regions. Indeed, it is thought that light forces, such as those produced by a repaired cleft lip, may be able to retard anterior development of the maxilla (Huang et al., 2002). These findings suggest that the maxillary complex is susceptible to therapeutic interventions.

Linton (1998) showed that patients with CLP have smaller SNA and SNB angles, compared with Class III patients. Thus, variability in mandibular form may represent developmental compensation to function during growth (Haskell, 1979). Singh et al. (1998, 2000b) have shown also that the mandible may contribute to the facial appearance of Class III malocclusion. In the present study, the NCC3 groups showed exuberant craniomandibular growth (≈60% increase in size), presumably associated with the phenotypic outcome. However, for the CLPC3 13- to 16-year group, FESA showed only approximately 30% increase in mandibular size. Thus, the final facial outcome observed in this group relied on deficient cranial base and midface development allied with normal mandibular growth. Postnatally, it is thought that the craniofacial region behaves as a complex adaptive system, which responds to functional stimuli, forming a functional matrix (Moss, 1997). Thus, light pressure from soft tissues may contribute to Class III malocclusion in children (Singh et al., 1999b, 1999c), including those with repaired CLP (Huang et al., 2002).

Overall, this study showed that the craniofacial development in NC children is significantly different from that of children treated for cleft lip and/or cleft palate, rejecting the null hypothesis tested. Surprisingly perhaps, the noncleft Class I and cleft Class I groups showed little qualitative differences in postnatal developmental patterns. This finding perhaps explains the retention of the Class I relationship in these cleft cases. Furthermore, the basis for Class III malocclusion development was not same for the NC patients and patients with cleft. Patients with cleft developed Class III malocclusion because of deficient development of the cranial base and midfacial areas, not because of excessive mandibular growth.

Finally, the soft tissue functional matrix that affects postsurgical craniofacial development in patients with CLP is another important concept that needs to be taken into consideration. Perhaps good functional habits and oral posture helped prevent cleft Class I groups from developing the Class III condition. On the other hand, we hypothesize that mouth breathing (because of nasal airway obstruction secondary to craniomaxillary deformity) might displace the tongue away from the repaired palate (Ren et al., 1992), inducing maxillary arch collapse in response to light lip pressure, thus precipitating a Class III condition. Recent studies are beginning to explore the use of growth guidance techniques such as nasoalveolar molding for correction of the dysfunctional nasal matrix in orofacial clefts in the early perinatal period. Thus, facial growth guidance remains a potential avenue for further research.

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