

Maxillomandibular and occlusal relationships in preadolescent patients with syndromic craniosynostosis treated by LeFort III distraction osteogenesis: 10-year surgical and phenotypic stability

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Introduction: LeFort III distraction osteogenesis may be indicated in the treatment of syndromic craniosynostosis with severe midface retrusion. This study investigates long-term changes in patients undergoing distraction as children, and compares outcomes to an unaffected, untreated control. **Methods:** Fifteen patients (9 males, 6 females) with syndromic craniosynostosis treated by LeFort III distraction at an average age of 4.9 ± 1.5 years were identified. Lateral cephalograms at predistraction, immediate, 1-, 5-, and 10-year postdistraction were superimposed using the best-fit of cranial base details. An untreated, unaffected matched control was obtained from the American Association of Orthodontists Foundation Legacy Collection. Differences in landmark location and cephalometric relationships were assessed between time points and between treatment and control groups. **Results:** LeFort III distraction produced an average advancement of 14.86 ± 5.14 mm at A-point and 10.54 ± 3.78 mm at orbitale. This advancement produced overcorrection of anteroposterior occlusal relationships and phenotypic correction of midface position. Surgical stability over a 10-year follow-up was excellent. Posttreatment growth was characterized by absent anteroposterior maxillary growth, preservation of dentoalveolar development and maxillary remodeling, and delayed mandibular growth. Subsequent growth resulted in a long-term phenotypic relapse of pretreatment Class III maxillomandibular relationship and negative overjet. **Conclusions:** LeFort III distraction osteogenesis produces stable advancement of the midface. Overcorrection is required for long-term phenotypic stability because of deficient postdistraction sagittal midface growth. Late mandibular growth contributes to underestimation of the amount of distraction required to produce long-term phenotypic correction. (Am J Orthod Dentofacial Orthop 2019;156:779-90)

Syndromic craniosynostosis describes a heterogeneous group of congenital craniofacial anomalies characterized by premature fusion of cranial sutures. The subsequent disruption in normal growth within the cranial base is frequently associated with a significant midface deficiency, requiring combined orthodontic–surgical treatment to address. LeFort III

distraction osteogenesis is 1 surgical technique used in the treatment of this midface deficiency and may be the treatment of choice in pediatric patients with severe deficiency, as greater advancement can be produced compared with conventional LeFort III advancement.¹ Additional reported benefits of LeFort III distraction over conventional advancement include eliminating the need for bone grafts and rigid fixation, a decrease in operative time and intraoperative bleeding, and reduced postoperative complications.^{2,3} As in conventional advancement, LeFort III distraction is most predictable if minimal growth potential remains at the time of treatment. However, distraction before the adolescent growth spurt is indicated in some patients, such as those exhibiting airway compromise, proptosis with risk of eye damage, and psychosocial

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concerns secondary to facial dysmorphism. Whereas LeFort III distraction is often conducted under the supervision of a cleft and craniofacial team, community orthodontists may be called upon to participate in the care of patients with syndromic craniosynostosis, particularly in regions where ready access to orthodontic treatment through a cleft and craniofacial team is limited, and when orthodontic treatment is required later in adolescence. As such, it is beneficial for the orthodontic practitioner to have an understanding of LeFort III distraction and subsequent long-term changes in patients with syndromic craniosynostosis.

Distraction osteogenesis has previously been demonstrated to produce stable advancement of the midface in preadolescent patients at 1- and 5-year follow-up,^{4,5} with no significant posterior movement of the advanced bony segment. Despite evidence of surgical stability, clinical examination at long-term follow-up often demonstrates a return of pretreatment phenotype, including concave profile, proptosis, dental Class III relationship, and anterior crossbite. This long-term “phenotypic relapse” has been attributed to the inherent maxillomandibular growth discrepancy in patients with craniosynostotic syndromes, which occurs in both untreated patients and those treated by conventional LeFort III advancement.⁶⁻⁹ As a result of the noted phenotypic relapse, some authors have advocated significant over advancement of the midface in patients with craniosynostosis undergoing LeFort III distraction with the goal of producing a long-term phenotype comparable with unaffected patients.¹⁰

In this study, we assessed maxillomandibular and dental relationships in patients with syndromic craniosynostosis treated by preadolescent LeFort III distraction. Postdistraction growth and craniofacial form were assessed over long-term follow-up and compared with an unaffected, untreated control group to differentiate mechanisms of postdistraction “relapse”. For the purposes of this study, “surgical relapse” is used to indicate posttreatment movement of surgically advanced structures in a direction opposing the surgical movement, relative to a stable reference landmark (cranial base), whereas “surgical stability” indicates the absence of such movements. In contrast, “phenotypic relapse” denotes a change in the relationship between surgically advanced structures and other craniofacial structures, which are not considered as stable landmarks because of anticipated growth or remodeling, toward their pre-surgical relationship. “Phenotypic stability” indicates the absence of such changes.¹¹ The purpose of this study, in differentiating phenotypic and surgical changes, was to provide a better understanding of the

postdistraction changes in patients with syndromic craniosynostosis, to provide clinical guidance in determining the magnitude of LeFort III advancement indicated in this patient population, and to suggest which methods are best used to assess appropriate midface advancement.

MATERIAL AND METHODS

This study was approved by the New York University Institutional Review Board. A retrospective review was conducted to identify patients with syndromic craniosynostosis treated by LeFort III distraction using a rigid external distraction device by a single surgeon (JGM). Patients were included in this study if LeFort III distraction was performed before age 10, and if clinical and radiographic follow-up was available at least 5 years after distraction. Patients were excluded if they had any additional surgical procedures to advance the maxilla or midface during the follow-up period. Fifteen patients were identified as meeting the inclusion criteria (9 males, 6 females) with diagnoses of Crouzon (n = 7), Apert (n = 6), and Pfeiffer (n = 2) syndromes, forming the treatment group. In all patients, preadolescent LeFort III distraction was indicated because of the diagnosis of moderate or severe pediatric obstructive sleep apnea (defined as an apnea hypopnea index >5, as assessed by polysomnography) or risk of corneal damage secondary to the inability to achieve palpebral closure.

Patients included in this study have also been included in previous reports.^{1,4,5,12} The surgical technique for LeFort III distraction in these patients has been previously described.^{1,4,5,12,13} In brief, after a standard subcranial LeFort III osteotomy¹⁴ and a 5-day latency, the midface was advanced using a rigid external distraction device anchored to an occlusal splint with or without zygomatic/maxillary anchor screws, activated at a rate of 0.5 mm twice per day. Appliance activation was continued until occlusal overcorrection at least 5-mm overjet was noted clinically. To correct exorbitism, activation was discontinued when the inferior orbital rim and anterior cornea were level in profile view.¹⁵

A chart review of patients meeting the inclusion criteria identified lateral cephalometric radiographs available for all patients at predistraction (T1), immediate postdistraction (T2), 1-year postdistraction (T3), and 5-year postdistraction (T4). Additionally, 12 patients had radiographs available at 10-year postdistraction (T5). A control group of age- and sex-matched dental Class I noncraniosynostotic individuals was obtained from the Oregon (Oregon Health and Sciences University) and Mathews' (University of California at San Francisco

School of Dentistry) growth studies through the American Association of Orthodontists Foundation Legacy Collection. There were no significant differences in age between treatment and control radiographs at any time point (Table I).

Lateral cephalograms in this study included analog and digital radiographs obtained using 4 different machines (2 in treatment group and 2 in control), all of known magnification. All radiographs were traced by a single examiner (TLG). Analog films were hand traced using a light box in a dark room, and tracings scanned into Dolphin Imaging (Dolphin Imaging and Management Solutions, Chatsworth, Calif) for digitizing. Digital radiographs were imported directly into Dolphin Imaging and traced in a dark room. All radiographs were corrected to a magnification of 0%. Standard cephalometric landmarks were identified, and linear and angular measures of dental and skeletal relationship measured (Fig 1, A-C). For radiographs with double images of bilateral structures, both images were traced, and the average position of the landmarks was used for data analysis. Tracings were superimposed on the sella-ethmoid region using the best-fit of cranial base details (structural method). Changes in landmark position were measured using an x,y coordinate system with sella as the origin, and 7° below the initial (T1) sella-nasion line as the horizontal plane. As nasion position is affected by LeFort III distraction, the horizontal reference plane was transferred to follow-up radiographs (T2-T5) by superimposition with the initial radiograph as described previously.

The effects of LeFort III distraction in the treatment group were assessed as changes in landmark location and cephalometric measures from T1 to T2 using paired sample *t* tests. "Surgical relapse" was defined as changes in landmark locations and cephalometric measures between immediate postdistraction (T2) and follow-up (T3, T4, and T5), assessed using paired sample *t* tests. "Phenotypic correction" was assessed by comparing treatment and control group differences at pre- and immediate postdistraction (T1, T2), and "phenotypic relapse" at follow-up (T3, T4, T5), using independent sample *t* tests. Statistical significance was defined as $P \leq 0.005$. Graphical representations of these analyses are provided in the form of composite cephalometric superimpositions for all time points in Figures 2-5. Quantitative data on landmark location are provided for initial (T1), immediate postdistraction (T2), and 10-year follow-up (T5) in Tables II-V. Landmark location data for interim follow-up time points (T3, T4) are available in the online Supplementary Tables (available at www.ajodo.org).

Method error was assessed by repeating tracing and superimposition of 30 randomly selected initial and

Table I. Patient and control ages

Time point	Treatment group age (y)	Control group age (y)	Significance
Initial (T1) (n = 15)	4.9 ± 1.5	4.9 ± 0.4	0.777
Postdistraction (T2) (n = 15)	5.1 ± 1.5	4.9 ± 0.4	0.531
1-year follow-up (T3) (n = 15)	6.2 ± 1.5	6.2 ± 0.3	0.958
5-year follow-up (T4) (n = 15)	10.0 ± 1.9	10.1 ± 0.4	0.834
10-year follow-up (T5) (n = 12)	15.3 ± 1.6	14.8 ± 0.5	0.239

Note. Values are mean ± standard deviation.

follow-up radiograph pairs 3 months after initial tracings. Correlation between initial and repeat measures ranged from 0.874 to 0.975, indicating excellent reproducibility.

RESULTS

Before LeFort III distraction, the treatment group demonstrated significantly greater midface retrusion by 13.45 ± 1.85 mm at ANS, 16.03 ± 1.72 mm at A-point, and 11.14 ± 1.58 mm at orbitale compared with the control group. A vertical maxillary deficiency of 3.99 ± 1.30 mm at A-point and 3.02 ± 1.44 mm at ANS was also observed, though the difference at ANS did not reach statistical significance ($P = 0.045$). The initial palatal plane in the treatment group was $5.32 \pm 6.39^\circ$ greater (clockwise rotation) than the control group ($P = 0.007$) (Fig 2; Table II).

LeFort III distraction (T2-T1) resulted in significant anterior movement of the midface by 13.81 ± 3.94 mm at ANS, 14.86 ± 5.31 mm at A-point, and 10.54 ± 3.78 mm at orbitale. A statistically nonsignificant trend to inferior maxillary displacement of 1.49 ± 3.94 mm at ANS ($P = 0.164$), 2.69 ± 3.74 mm at A-point ($P = 0.014$), and a $5.09 \pm 6.74^\circ$ counterclockwise rotation of the palatal plane ($P = 0.011$) were also observed (Fig 3, A; Table II). These changes resulted in a phenotypic correction of the midface position, with no statistically significant differences between control and treatment groups immediately after distraction (T2) (Fig 3, B; Table II).

Over the 10-year postdistraction follow-up period, excellent surgical stability was observed with no evidence of relapse in maxillary position (Fig 4). A statistically nonsignificant downward and forward movement of ANS position in the treatment group was observed from T2 to T5, as was a statistically significant inferior displacement of A-point (5.59 ± 2.50 mm, $P = 0.000$)

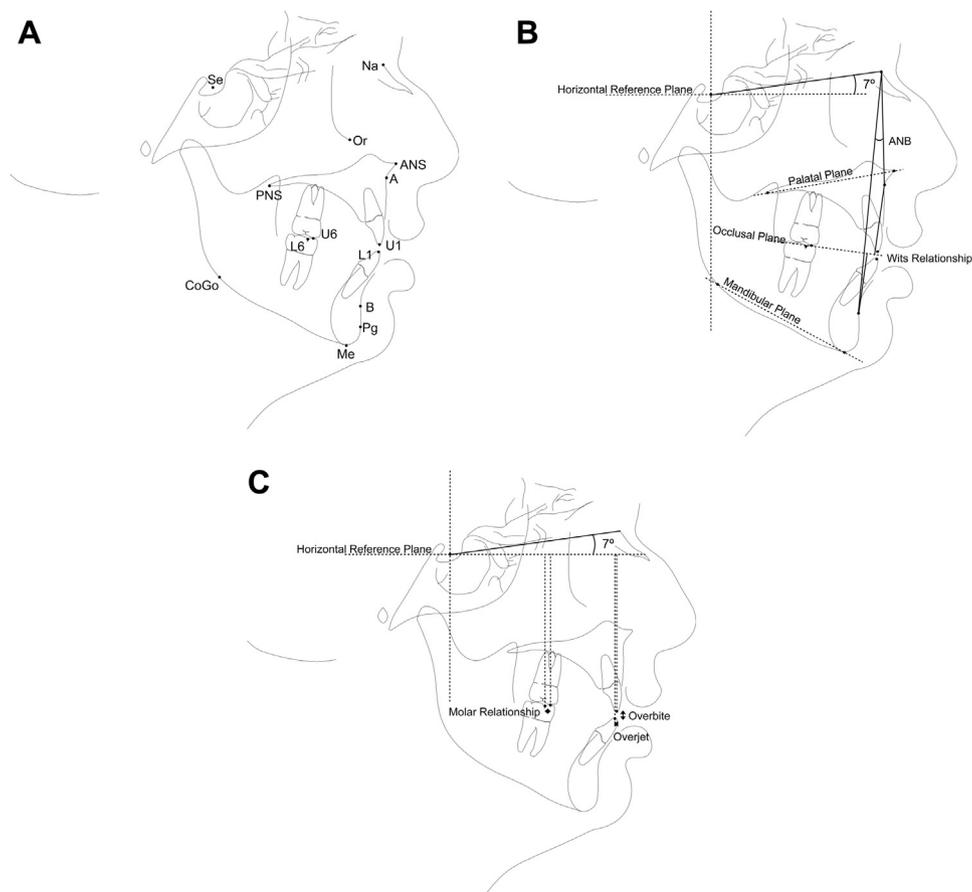


Fig 1. A, Cephalometric landmarks; B, skeletal relationships; C, dental relationships.

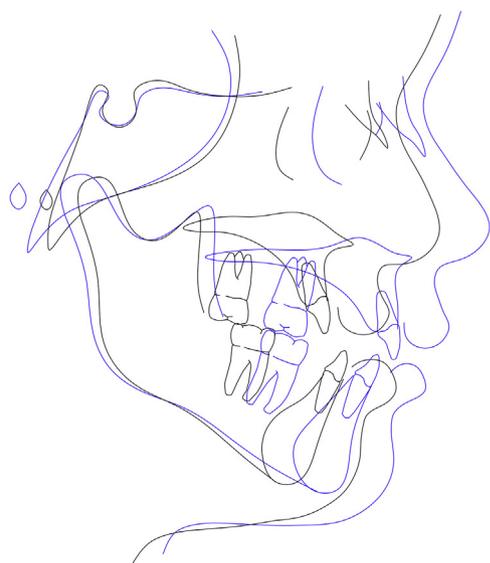


Fig 2. Initial composite cephalometric forms of the treatment group before distraction (T1, black) and the control group (T1, blue).

consistent with continued dentoalveolar development (Table II). These changes were significantly less than those observed in the control group, ultimately resulting in a long-term phenotype characterized by a retrusive and vertically deficient maxillary position in the treatment group when compared with the control group (Fig 5). Orbitale position in the treatment group exhibited a statistically nonsignificant trend to inferior displacement (-2.80 ± 3.26 mm, $P = 0.013$) from T2 to T5, while remaining stable anteroposteriorly. During the same time period, the control group demonstrated significant anterior displacement of orbitale (7.11 ± 2.00 mm, $P = 0.000$), ultimately resulting in a significantly more retrusive orbitale in the treatment group than the unaffected control group at T5 (-7.83 ± 1.63 mm, $P = 0.000$).

No statistically significant differences were observed in mandibular measures between the treatment group and the control group at T1, though there was a trend to more retrusive mandibular position at B-point (-6.85 ± 3.09 mm, $P = 0.035$), pogonion (-8.93 ± 3.44 mm, $P = 0.015$), and menton

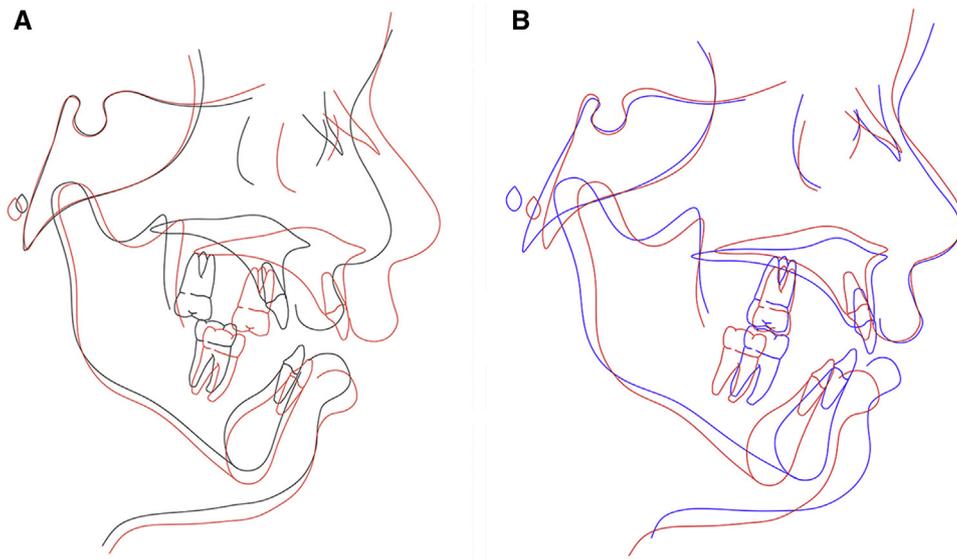


Fig 3. **A**, Comparison of composite cephalometric forms of treatment group before (T1, *black*) and after distraction (T2, *red*). **B**, Phenotypic correction; comparison of the treatment group after distraction (T2, *red*) with the control group (T1, *blue*).

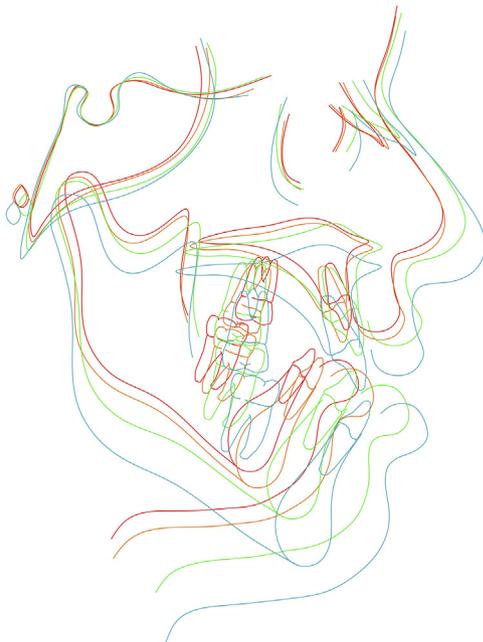


Fig 4. Surgical stability composite cephalometric tracings. Treatment group immediately after distraction (T2, *red*) compared with follow-up at 1 year (T3, *orange*), 5 years (T4, *green*), and 10 years (T5, *teal*).

(-9.85 ± 3.39 mm, $P = 0.007$) and a steeper mandibular plane angle (5.38 ± 2.06 mm, $P = 0.014$) in the treatment group (Fig 2; Table III). LeFort III distraction resulted in mandibular opening secondary to downward

displacement of the midface. Significant inferior displacement of pogonion (-3.57 ± 3.16 mm, $P = 0.001$) and menton (-3.13 ± 2.63 mm, $P = 0.000$) was observed, though there was no significant change in mandibular plane angle ($+1.05 \pm 3.97$, $P = 0.325$) (Fig 3, A; Table III).

Significant mandibular growth in the downward and forward direction was observed in both the treatment group (Fig 4) and control group over the 10-year follow-up period. Patients with craniosynostosis exhibited greater anterior displacement at B-point (mean difference of 4.81 mm), pogonion (mean difference of 5.20 mm), and menton (mean difference of 6.48 mm) during the follow-up period and a tendency to counterclockwise rotation of the mandibular plane ($-5.92 \pm 7.44^\circ$, $P = 0.019$) (Table III). These differences in mandibular growth magnitude and rotation resulted in the elimination of the noted T1 trend to a retrusive mandible and steeper mandibular plane in the treatment group by 10-year follow-up (Fig 5, C).

The initial maxillomandibular relationship in the craniosynostotic group was significantly Class III as assessed by both ANB ($-6.23 \pm 4.49^\circ$) and Wits relationship (-7.16 ± 3.90 mm), whereas the control group demonstrated a tendency toward a Class II relationship at T1 (Fig 2; Table IV). LeFort III distraction in the treatment group resulted in statistically significant increases in both ANB ($+17.87 \pm 7.01^\circ$, $P = 0.000$) and Wits relationship ($+14.15 \pm 6.51$ mm, $P = 0.000$) (Fig 3, A). This represented a significant

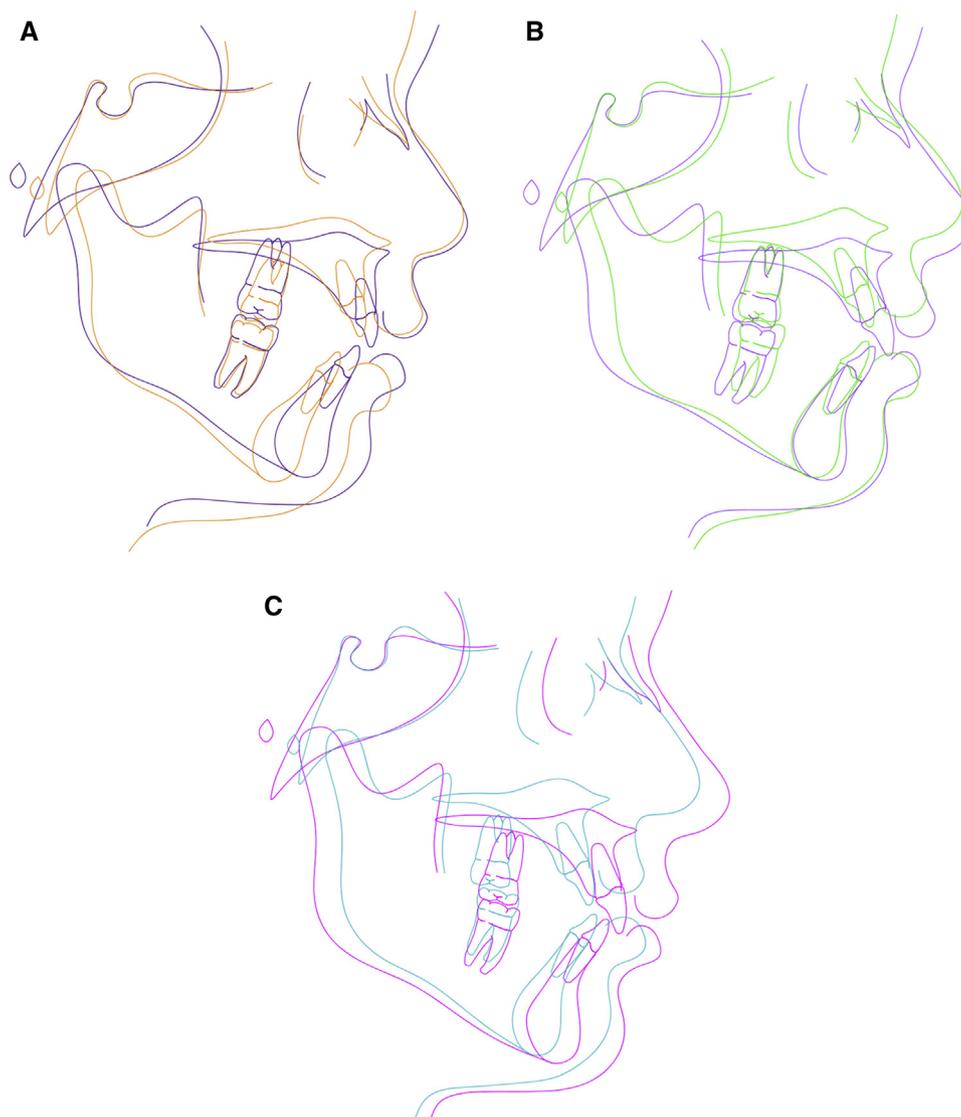


Fig 5. Phenotypic stability composite cephalometric tracings. **A**, Treatment group 1-year postdistraction (T3, orange) compared with control group (T3, dark purple). **B**, Treatment group 5-year postdistraction (T4, green) compared with control group (T4, light purple). **Right**, Treatment group 10-year postdistraction (T5, teal) compared with control group (T5, pink).

overcorrection in the maxillomandibular relationship, with the treatment group demonstrating an ANB $5.71 \pm 1.88^\circ$ ($P = 0.005$) greater than the control group immediately after distraction (T2) (Fig 3, B).

Over the 10-year follow-up period, maxillomandibular relationship in the control group was maintained. The treatment group demonstrated significant change toward their initial Class III relationship in both ANB ($-9.59 \pm 6.42^\circ$, T2-T5, $P = 0.000$) and Wits relationship (-12.06 ± 5.02 mm T2-T5, $P = 0.000$) (Fig 4). At 10-year follow-up, the treatment group maintained a positive ANB angle on average ($0.99 \pm 6.26^\circ$), though

the Wits relationship demonstrated a significant Class III relationship (-4.96 ± 5.89 mm) (Fig 5, C; Table IV).

Initial dental relationships in treatment group were characterized by Class III molar relationship (-6.14 ± 3.04 mm), anterior crossbite (overjet -4.64 ± 2.81 mm), and open bite (overbite -3.98 ± 2.68 mm) (Table IV). LeFort III distraction significantly improved anteroposterior dental relationships with an average overjet increase of 12.70 ± 4.54 mm ($P = 0.000$) and molar relationship of 11.83 ± 5.28 mm ($P = 0.000$) and produced no significant change in overbite (Fig 3, A). These changes

Table II. Midface position and angulation

Cephalometric Measures	Group	T1	Sig	T2	Treatment		T5	10 y	
					(T2-T1)	Sig		(T5-T2)	Sig
Or (x, mm)	TG (SD)	40.19 (4.75)		50.73 (4.52)	10.54 (3.78)	0.000	51.02 (4.61)	-0.26 (1.90)	0.646
	CG (SD)	51.33 (3.86)		51.33 (3.86)	N/A		58.85 (3.71)	7.11 (2.00)	0.000
	TG-CG(SEM)	-11.14 (1.58)	0.000	-0.60 (1.54)		0.699	-7.83 (1.63)		0.000
Or (y, mm)	TG (SD)	-15.77 (4.13)		-17.94 (5.24)	-2.17 (2.74)	0.008	-21.92 (4.11)	-2.80 (3.26)	0.013
	CG (SD)	-16.83 (1.73)		-16.83 (1.73)	N/A		-20.21 (2.90)	-3.34 (2.13)	0.000
	TG-CG(SEM)	1.06 (1.16)	0.367	-1.11 (1.43)		0.441	-1.70 (1.38)		0.229
ANS (x, mm)	TG (SD)	53.93 (4.80)		67.74 (6.52)	13.81 (3.94)	0.000	72.12 (5.86)	4.00 (6.05)	0.043
	CG (SD)	67.37 (5.32)		67.37 (5.32)	N/A		78.51 (6.15)	10.89 (3.86)	0.000
	TG-CG(SEM)	-13.45 (1.85)	0.000	0.37 (2.17)		0.867	-6.39 (2.37)		0.013
ANS (y, mm)	TG (SD)	-30.49 (4.50)		-31.99 (4.90)	-1.49 (3.94)	0.164	-36.22 (5.59)	-3.83 (4.14)	0.008
	CG (SD)	-33.51 (3.29)		-33.51 (3.29)	N/A		-46.92 (4.48)	-13.24 (2.44)	0.000
	TG-CG(SEM)	3.02 (1.44)	0.045	1.53 (1.52)		0.325	10.70 (1.98)		0.000
A-point (x, mm)	TG (SD)	47.69 (4.91)		62.55 (6.31)	14.86 (5.14)	0.000	65.08 (6.68)	2.38 (5.66)	0.173
	CG (SD)	63.71 (4.50)		63.71 (4.50)	N/A		71.76 (4.84)	7.88 (1.77)	0.000
	TG-CG(SEM)	-16.03 (1.72)	0.000	-1.17 (2.00)		0.564	-6.67 (2.26)		0.007
A-point (y, mm)	TG (SD)	-33.79 (4.03)		-36.49 (4.80)	-2.69 (3.74)	0.014	-42.48 (5.32)	-5.59 (2.50)	0.000
	CG (SD)	-37.78 (3.01)		-37.78 (3.01)	N/A		-52.22 (4.93)	-14.29 (2.94)	0.000
	TG-CG(SEM)	3.99 (1.30)	0.005	1.29 (1.46)		0.384	9.75 (2.01)		0.000
Palatal plane (°)	TG (SD)	5.32 (6.39)		0.23 (7.63)	-5.09 (6.74)	0.011	-4.14 (3.67)	-4.80 (5.88)	0.016
	CG (SD)	0.00 (3.02)		0.00 (3.02)	N/A		1.00 (3.51)	1.12 (2.48)	0.114
	TG-CG(SEM)	5.32 (1.82)	0.007	0.23 (2.12)		0.916	-5.14 (1.41)		0.001

Sig, significance; SEM, standard error of the mean; SD, standard deviation.

Table III. Mandibular position and angulation

Cephalometric Measures	Group	T1	Sig	T2	Treatment		T5	10 y	
					(T2-T1)	Sig		(T5-T2)	Sig
B-point (x, mm)	TG (SD)	47.09 (9.58)		47.76 (9.60)	0.67 (5.03)	0.616	62.58 (11.85)	14.00 (7.46)	0.000
	CG (SD)	53.94 (7.14)		53.94 (7.14)	N/A		63.68 (5.84)	9.19 (3.70)	0.000
	TG-CG(SEM)	-6.85 (3.09)	0.035	-6.18 (3.09)		0.055	-1.10 (3.58)		0.761
B-point (y, mm)	TG (SD)	-72.31 (6.95)		-75.25 (7.25)	-2.95 (5.23)	0.047	-90.37 (9.71)	-13.87 (7.27)	0.000
	CG (SD)	-73.79 (5.52)		-73.79 (5.52)	N/A		-92.26 (8.92)	-18.61 (5.09)	0.000
	TG-CG(SEM)	1.48 (2.29)	0.524	-1.47 (2.35)		0.538	1.90 (3.65)		0.608
Pg (x, mm)	TG (SD)	43.47 (10.56)		43.64 (10.66)	0.17 (4.93)	0.898	62.04 (13.98)	16.99 (8.69)	0.000
	CG (SD)	52.40 (8.11)		52.40 (8.11)	N/A		64.86 (7.44)	11.78 (3.76)	0.000
	TG-CG(SEM)	-8.93 (3.44)	0.015	-8.76 (3.46)		0.017	-2.82 (4.30)		0.519
Pg (y, mm)	TG (SD)	-82.43 (5.46)		-86.00 (5.02)	-3.57 (3.16)	0.001	-105.58 (10.04)	-18.90 (8.20)	0.000
	CG (SD)	-83.35 (6.41)		-83.35 (6.41)	N/A		-106.36 (9.68)	-22.89 (5.37)	0.000
	TG-CG(SEM)	0.93 (2.17)	0.673	-2.65 (2.10)		0.218	0.77 (3.87)		0.843
Me (x, mm)	TG (SD)	36.12 (10.18)		36.25 (10.52)	0.13 (5.19)	0.926	54.58 (15.02)	17.03 (9.63)	0.000
	CG (SD)	45.97 (8.27)		45.97 (8.27)	N/A		57.19 (7.82)	10.55 (4.11)	0.000
	TG-CG(SEM)	-9.85 (3.39)	0.007	-9.72 (3.46)		0.009	-2.61 (4.60)		0.575
Me (y, mm)	TG (SD)	-84.99 (5.68)		-88.11 (5.63)	-3.13 (2.63)	0.000	-110.43 (9.44)	-21.36 (7.85)	0.000
	CG (SD)	-87.37 (6.39)		-87.37 (6.39)	N/A		-113.99 (9.72)	-26.30 (4.80)	0.000
	TG-CG(SEM)	2.39 (2.21)	0.289	-0.74 (2.20)		0.739	3.56 (3.77)		0.355
Mandibular plane (°)	TG (SD)	36.20 (6.26)		37.25 (6.70)	1.05 (3.97)	0.325	30.96 (9.71)	-5.92 (7.44)	0.019
	CG (SD)	30.83 (4.94)		30.83 (4.94)	N/A		27.74 (5.68)	-2.87 (2.79)	0.002
	TG-CG(SEM)	5.38 (2.06)	0.014	6.42 (2.15)		0.006	3.22 (3.06)		0.304

Sig, significance; SEM, standard error of the mean; SD, standard deviation.

represent a significant overcorrection in the anteroposterior dental relationship; immediately after distraction (T2), the treatment group demonstrated a greater overjet

(+4.34 ± 1.41 mm, *P* = 0.005) and Class II molar relationship (+5.30 ± 1.44 mm, *P* = 0.005) than the control group (Fig 3, B).

Table IV. Maxillomandibular relationship

Cephalometric Measures	Group	T1	Sig	T2	Treatment		T5	10 y	
					(T2-T1)	Sig		(T5-T2)	Sig
ANB (°)	TG (SD)	-6.23 (4.49)		11.65 (6.75)	17.87 (7.01)	0.000	0.99 (6.26)	-9.59 (6.42)	0.000
	CG (SD)	5.93 (2.70)		5.93 (2.70)	N/A		4.26 (1.92)	-1.55 (2.89)	0.066
	TG-CG(SEM)	-12.16 (1.35)	0.0000	5.71 (1.88)		0.005	-3.27 (1.76)		0.076
Wits (mm)	TG (SD)	-7.16 (3.90)		6.99 (6.69)	14.15 (6.51)	0.000	-4.96 (5.89)	-12.06 (5.02)	0.000
	CG (SD)	1.57 (2.78)		1.57 (2.78)	N/A		2.19 (2.40)	0.75 (2.93)	0.355
	TG-CG(SEM)	-8.73 (1.24)	0.0000	5.43 (1.87)		0.007	-7.14 (1.72)		0.000

Sig, significance; SEM, standard error of the mean; SD, standard deviation.

Table V. Dental relationships

Cephalometric Measures	Group	T1	Sig	T2	Treatment		T5	10 y	
					(T2-T1)	Sig		(T5-T2)	Sig
Overbite (mm)	TG (SD)	-3.98 (3.22)		-5.16 (5.29)	-1.18 (4.83)	0.360	-2.52 (3.83)	2.98 (7.70)	0.206
	CG (SD)	1.08 (2.68)		1.08 (2.68)	N/A		3.87 (2.68)	2.64 (2.97)	0.005
	TG-CG(SEM)	-5.06 (1.08)	0.000	-6.24 (1.53)		0.000	-6.39 (1.28)		0.000
Overjet (mm)	TG (SD)	-4.64 (2.81)		8.06 (4.95)	12.70 (4.54)	0.000	-2.72 (6.33)	-10.65 (6.22)	0.000
	CG (SD)	3.72 (2.28)		3.72 (2.28)	N/A		3.59 (1.74)	-0.11 (2.10)	0.842
	TG-CG(SEM)	-8.36 (0.93)	0.000	4.34 (1.41)		0.005	-6.31 (1.76)		0.001
Molar relationship (mm)	TG (SD)	-6.14 (3.04)		5.69 (5.39)	11.83 (5.28)	0.000	-2.90 (6.48)	-8.28 (6.27)	0.001
	CG (SD)	-0.39 (1.43)		0.39 (1.43)	N/A		-1.24 (1.72)	-1.69 (2.16)	0.012
	TG-CG(SEM)	-5.75 (0.87)	0.000	5.30 (1.44)		0.001	-1.66 (1.93)		0.404
Occlusal plane (°)	TG (SD)	12.09 (6.28)		8.19 (9.37)	-3.90 (9.80)	0.146	8.18 (6.00)	1.46 (8.00)	0.539
	CG (SD)	12.61 (5.36)		12.61 (5.36)	N/A		9.53 (4.36)	-2.76 (2.95)	0.004
	TG-CG(SEM)	-0.51 (2.13)	0.812	-4.41 (2.79)		0.125	-1.35 (2.04)		0.515

Sig, significance; SEM, standard error of the mean; SD, standard deviation.

Dental relationships in the control group at 1-, 5-, and 10-year follow-up were generally stable, with the only significant changes detected being a 10-year overbite increase of 2.64 ± 2.97 mm ($P = 0.005$) and a counter-clockwise rotation of the occlusal plane ($2.76 \pm 2.95^\circ$, $P = 0.004$). Conversely, in the treatment group, significant postdistraction changes toward the initial anteroposterior relationship were detected at both 5-year and 10-year follow-up (Fig 4). From T2 to T5, overjet decreased by 10.65 ± 6.22 mm, and molar relationship by 8.28 ± 6.27 mm. This ultimately resulted in a significant T5 difference in overjet between treatment and control groups of -6.31 ± 1.76 mm ($P = 0.001$) (Fig 5, C). Anterior open bite was observed in the treatment group at all time points, with significant intergroup differences between treatment and control groups detected consistently at all time points. Occlusal plane angulation did not differ between treatment and control groups at any time point.

DISCUSSION

The purpose of this study was to assess the skeletal and dental relationships in a longitudinally-followed

sample of patients with syndromic craniosynostosis who were treated by LeFort III distraction osteogenesis before age 10 years. To differentiate surgical relapse from posttreatment changes caused by the growth pattern characteristic of syndromic craniosynostosis^{6,9} (phenotypic relapse), subjects with craniosynostosis were compared with an age- and sex-matched control group of unaffected, untreated Class I subjects. To our knowledge, this represents the longest longitudinal follow-up in this patient population published to date.

Before LeFort III distraction, patients with craniosynostosis demonstrated maxillary deficiency in the vertical and anteroposterior planes compared with the unaffected control group and a significant Class III skeletal relationship as assessed by both ANB angle and Wits relationship. Both the maxillary and mandibular plane angles were steeper in the craniosynostotic group. These differences are consistent with previous reports.^{6,8,9,16} The initial dental relationships in our study were consistent with underlying the Class III skeletal relationships; patients with craniosynostosis predistraction demonstrated significantly more negative overbite, overjet, and molar relationships than the control group (Table V).

Additionally, the craniosynostotic group was noted predistracted to have a greater mandibular retrusion by 6.18 ± 3.09 mm at B-point, 8.76 ± 3.46 mm at pogonion, and 9.72 ± 3.46 mm at menton. These differences were borderline nonsignificant, likely because of high individual variation in mandibular position in both the treatment and control groups. Previous reports on mandibular length and position in subjects with craniosynostosis are varied, and their interpretation complicated by the use of different cephalometric measures. Mandibular length has been reported to be normal or mildly reduced, with an increased ramus height to body length ratio,¹⁷⁻²⁰ and mandibular prominence, as assessed by angular measures to cranial base, normal or mildly increased.²⁰⁻²² Neither of these measures are ideal, as their interpretation may be confounded by differences in cranial base morphology and condyle location. In this study, we have attempted to limit these confounders by the use of a coordinate system and cephalometric superimpositions.

LeFort III distraction produced an average midface advancement of approximately 15 mm at A-point and 10.5 mm at orbitale, with a concurrent small inferior displacement of 2-3 mm. There was a concurrent mild opening of the mandible, as evidenced by inferior displacement of the pogonion and menton, though no significant change in the mandibular plane angle was detected, indicating good vertical control of the LeFort III segment during distraction.²³ A modest unfavorable counterclockwise rotation of the LeFort III segment of approximately 5° was noted during distraction. In this patient sample, the endpoint of distraction was determined by a standardized clinical protocol of occlusal overcorrection to a positive overjet of at least 5 mm. The goal of this protocol was to produce modest overcorrection in midface advancement to compensate for an anticipated future maxillary growth deficiency.^{6,9,16} Comparison with the unaffected, untreated control group demonstrated that this occlusal overcorrection resulted in a maxillary position which was within normal limits, but did not produce the intended overcorrection (Fig 3, B). Because of the initial mandibular retrusion noted in the craniosynostotic treatment group as compared with controls, the occlusal relationship underestimated the magnitude of skeletal midface overcorrection required relative to cranial base. This finding suggests that determining midface position in LeFort III distraction by occlusal relationship may underestimate the degree of overcorrection achieved relative to an unaffected phenotype.

Surgical stability and relapse was assessed in this study by comparing cephalometric measures and landmark positions between immediate postdistracted (T2)

and 1-, 5-, and 10-year follow-up (T3, T4, T5, respectively). Excellent surgical stability was observed in the majority of patients. At 1-year postdistracted, no significant posterior displacement in midface position, assessed at orbitale, ANS, or A-point, was observed, and only 2 patients exhibited posterior movement at A-point of >2 mm (-2.20 and -3.30 mm). Surgical stability was maintained at both 5- and 10-year follow-up with no significant anteroposterior changes at orbitale, ANS, or A-point. These findings are consistent with previous reports, which have assessed surgical stability of midface distraction by various techniques between 1- and 5- year follow-up.^{1,3-5,16,24-29} A recent systematic review, which included 9 studies on LeFort III distraction osteogenesis, concluded that midface relapse was typically $<10\%$ of the surgical movement at 1-3-year follow-up, a finding again consistent with the results of our study.¹¹

Phenotypic relapse and stability was assessed in this study by comparing the postdistracted, craniosynostotic treatment group at T3, T4, and T5 with longitudinal records of an age- and sex-matched control group of unaffected, untreated Class I subjects from the Oregon and Mathews' growth studies. As noted previously, at immediate postdistracted (T2), phenotypic correction of the midface position was observed, with no differences between treatment and control groups. However, owing to the tendency to a more retrusive mandibular position and steeper mandibular plane in the treatment group, this correction of maxillary position was associated with apparent overcorrection of maxillomandibular and dental relationships to a significant Class II relationship, with statistically significantly greater ANB angle, overjet, and Class II molar relationship than the control group.

Over the 10-year follow-up, inferior movement of the maxilla at A-point of approximately 1.5 mm was observed, and serial cephalometric superimposition demonstrated continued maxillary dental eruption and inferior displacement of the maxilla consistent with dentoalveolar growth and maxillary remodeling. Wits relationship, ANB angle, molar relationship, and overjet were all maintained at 1-year postdistracted. At 5- and 10-year postdistracted, the same pattern of downward maxillary remodeling was observed. Minimal anterior displacement of maxillary position occurred over the 10-year follow-up period, consistent with an absence of normal sutural or displacement growth of the midface in patients with syndromic craniosynostosis. This pattern of midface growth in patients with syndromic craniosynostosis has been previously reported in both treated^{6,8,9,16,26,30-33} and untreated⁹ patients. Midface growth during the follow-up period as assessed

at orbitale presented a similar pattern. Both the treatment and control groups exhibited approximately 2–3-mm inferior displacement at orbitale, with no significant differences between the groups. Anteroposteriorly, patients with craniosynostosis in the treatment group exhibited no significant anteroposterior changes, whereas the control group demonstrated significant anterior movement at orbitale, ultimately resulting in phenotypic relapse of orbital retrusion as assessed at orbitale. These cephalometric differences were clinically relevant, as they were associated with both a recurrence in proptosis³⁴ and the anticipated need for subsequent surgical midface advancement at the LeFort III level following growth completion in approximately two thirds of the treatment group.

Significant downward and forward mandibular growth occurred in subjects with craniosynostosis over the 10-year follow-up. Coupled with the lack of anteroposterior maxillary growth, this continued mandibular growth led to phenotypic relapse of both skeletal and dental relationships. By 10 years after distraction, the treatment group exhibited a significantly more Class III skeletal relationship than the control group as assessed by Wits relationship and a statistically significantly more negative overjet. Molar relationship did not differ significantly between groups, though this is likely due to orthodontic treatment during the follow-up period. Orthodontic tooth movement would be expected to contribute to variability in molar position depending on individual patient considerations such as extractions and anchorage reinforcement.

Although the difference in mandibular growth between the treatment group and control group from T2–T5 was not statistically significant, there was a tendency for a greater magnitude and more horizontal direction of growth in the treatment group. Between T2 and T5, mandibular position at B-point moved an average of 14.00 mm anteriorly and 13.87 mm inferiorly in the treatment group compared with 9.19 mm anteriorly and 18.61 mm inferiorly in the control group. The mandibular plane angle closed by an average of 5.92° in the treatment group as compared with 2.87° in the control group. As a result of these differences, the pretreatment tendency to a more retrusive mandibular position in the treatment group was no longer present at T5. This trend indicates that syndromic craniosynostosis may also have an impact on mandibular growth, with adolescent “catch-up” growth eliminating the mandibular retrognathia noted at the initial preadolescent assessment. Taken in combination with the significant individual variation in mandibular position observed in this study, these findings indicate that occlusal relationships are an unreliable indicator for determining the end

point of activation (overcorrection) in LeFort III distraction, particularly in young patients. Comparison of patient cephalometric tracings during distraction with reference standards may be a more reliable method, though limiting radiation exposure when using repeated radiographic assessments (rather than clinical measures) is an important consideration. Additionally, the relationship between the globe and bony orbit is an important consideration in determining distraction end point in order to prevent the development of an enophthalmic postdistraction relationship. Further research to determine the best measures of midface position and the degree of overcorrection indicated to produce long-term phenotypic stability would be of clinical benefit in treatment planning.

Our study was limited by its retrospective nature and small sample size. The low prevalence of syndromic craniosynostosis and the difficulty in ensuring patient follow-up 10 years after surgical intervention, combined to limit the available patient sample. Loss of patients also introduces a risk of systematic bias. However, loss to follow-up in this study was relatively low, with all patients who received preadolescent LeFort III distraction returning for 1- and 5-year follow-up, and only 3 lost at 10-year follow-up. Additionally, owing to the paucity of eligible participants, the treatment group represents a heterogeneous group with respect to both syndromic diagnosis and race. Finally, whereas the inclusion of an unaffected control group allows for better characterization of phenotypic changes in the treatment group, it should be noted that the control group is historical in nature, and as such, the conclusions of this study may be confounded by secular growth trends.

CONCLUSIONS

Preadolescent patients with syndromic craniosynostosis treated by LeFort III distraction were followed longitudinally by cephalometric superimposition for up to 10 years, and compared with an untreated, unaffected control. Surgical and phenotypic stability were assessed and long-term growth disturbances characterized.

- (1) Surgical stability was excellent, with no significant anteroposterior changes in midface position noted 10 years after LeFort III distraction.
- (2) Preadolescent patients with syndromic craniosynostosis presented with mandibular retrognathia relative to unaffected controls. Adolescent mandibular growth eliminated this difference by the 10-year follow-up and combined with deficient anteroposterior maxillary growth to produce long-term phenotypic relapse. Greater overcorrection of

midface position during distraction will be required to produce long-term phenotypic stability.

- (3) Clinical measurement of dental relationships is an unreliable indicator in determining the distraction end point because of a tendency of mandibular retrusion in younger patients with craniosynostosis. Cephalometric superimposition with an untreated, unaffected reference standard as performed in this study represents a novel approach and may prove to be a more reliable determinant of desired postdistraction midface position in the future. Further research in this area is required before more definitive recommendations can be made.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ajodo.2018.12.022>.

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