Craniofacial team management in Apert syndrome

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Introduction: Apert syndrome is one of the rarest of the craniosynostosis syndromes. Affected persons have extensive structural and functional impairments, some of which can be life threatening. Management requires team care from infancy to adulthood. The purposes of this article are to assess the outcomes in individuals with Apert syndrome after completion of treatment and to review current protocols for craniofacial team care and dental, orthodontic, and orthognathic surgical management. **Methods:** This was a retrospective cohort study of 8 subjects with Apert syndrome. Cephalograms at 2 time points were compared: adolescence (before midface advancement) and at least 1 year after advancement. The cephalometric values were compared with paired *t* tests. Team protocols are delineated. **Results:** Measurements indicating forward positioning of the maxilla increased significantly: SNA by 10.7° ($P = 0.002$) and midface length by 9.6 mm ($P = 0.002$). Sagittal jaw relationship improved significantly as well: ANB by 14° ($P = 0.004$) and the Wits appraisal by 8 mm ($P = 0.003$). Vertical dimensions also increased. **Conclusions:** All individuals had significantly improved and stable positions of the midface and normalized facial profiles after treatment. (Am J Orthod Dentofacial Orthop 2012;141:S82-7)

Apert syndrome (OMIM [Online Mendelian Inheritance in Man] #101200) is a rare craniosynostosis syndrome with an estimated incidence of 1 in every 160,000 live births; it accounts for 4% to 5% of all craniosynostosis syndromes. The syndrome is characterized by irregular craniosynostosis, midface hypoplasia, and syndactyly of the fingers and toes.[1] Although most are sporadic, many are associated with high paternal age.[2,3] The disorder is associated with a mutation in the FGFR2 gene that maps to chromosome 10q25-10q26 and follows an autosomal dominant inheritance pattern.[4] The recurrence risk for an unaffected parent of a child with Apert syndrome is minor, but an affected person has a 50% risk of having a baby with the syndrome.

The sagittal and metopic sutures are incompletely formed, often with a broad defect in the midline from glabella to the posterior fontanel that might gradually fill in over time.[5,6] The premature suture closures can result in acrobrachycephaly or turribrachycephaly, large, late-closing fontanels, and macrocephaly. Premature fusion might restrict brain growth and central nervous system development. Those with Apert syndrome have been reported to have a mean IQ of 74 and significant mental deficiencies not readily explained by suture closures. Other central nervous system characteristics include agenesis of the corpus callosum, ventriculomegaly, and hydrocephalus. Spinal fusions are frequently found in C3-4 and C5-6. If there is synostosis of the radius and humerus, limb mobility might be limited.[1]

The maxilla is retruded and hypoplastic. and the palate is high arched and narrow with bulbous palatal swellings, mostly consisting of mucopolysaccharides. This excessive soft-tissue buildup can give the appearance of a pseudocleft. A 30% incidence of soft-palate clefting has been reported.[7] Other findings include shallow orbits, hypertelorism, down-slanting palpebral

Table I. Number, age, and sex of subjects at both time points

	T1	*T2*
Mean age	14.9 y	17.9 y
Age range	13-16 y	15-20 y
Sex	1 male, 7 females	1 male, 7 females

T1, Before surgery; *T2*, time point farthest from surgery.

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Table II. Abbreviations, descriptions, and definitions of points and measurements used on lateral cephalograms

Abbreviation	*Description*	*Definition*
A	A-point	Deepest point of the curve of the maxilla, between anterior nasal spine (ANS) and the dental alveolus
B	B-point	Most posterior point in the concavity along the anterior border of the symphysis
ANS	Anterior nasal spine	The tip of the anterior nasal spine
PNS	Posterior nasal spine	The tip of the posterior nasal spine
Ba	Basion	Most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen
Ar	Articulare	Posterior border of the condyle
Co	Condylion	Most posterior superior point of the condyle
Me	Menton	Most interior point of the symphysis of the mandible
Pg	Pogonion	Most anterior point of the mandible
OP	Occlusal plane	Functional occlusal plane located between the first molars and the first premolars
PT	Pterygomaxillary fissure point	Intersection of the inferior border of the foramen rotundum with the posterior wall of the pterygomaxillary fissure
Or	Orbitale	Lowest point of the orbital rim
S	Sella	Center of the pituitary fossa of the sphenoid bone
N	Nasion	Intersection of theinternasal suture with the frontonasal suture in the \midsagittal plane
Gn	Gonion	Most convex point along the inferior border of the ramus
SNA	Maxillary prognathism	Angle formed between sella, nasion, and A-point
N-A	Maxillary prognathism	Linear measurement between nasion perpendicular and A-point
N-B	Mandibular prognathism	Linear measurement between nasion perpendicular and B-point
SNB	Mandibular prognathism	Angle formed between sella, nasion, and B-point
N-Pg	Mandibular prognathism	Linear measurement between nasion perpendicular and B-point
ANB	Sagittal jaw relationship	Angle formed between A-point, nasion, and B-point
MP-SN	Mandibular plane angle	Angle formed between the mandibular plane and the sella-nasion plane
MP	Mandibular plane	Plane from menton to gonion
OP-SN	Occlusal plane-sella-nasion	Angle formed between the occlusal plane and the sella-nasion plane
FMA	Mandibular plane angle	Angle formed between the Frankfort horizontal plane and the mandibular plane
Y-axis	Y-axis	Angle formed between S-Gn and S-N
LFH	Lower face height	Linear measurement of ANS-Me
A-Po	Lower incisor protrusion	Linear measurement of lower incisor tip to A-Po line
E-plane	Ricketts' E-line	Line between the nasal tip and soft-tissue chin point
Palate plane	Palatal plane	
U1	Upper incisor	Tip of the maxillary central incisor edge
L1	Lower incisor	Tip of the mandibular central incisor edge

fissures, strabismus, proptosis, depressed nasal bridge, and deviated nasal septum. Chronic otitis media, hearing loss, and abnormal semicircular canals are common findings. Increased ocular pressure can result in blindness.[1]

Both the primary and permanent dentitions are characterized by impaction, severe crowding, delayed eruption, thick gingival swellings, and congenitally missing teeth. The development of the primary dentition is delayed by a year (mean, 0.96 years), with increased delays in dental development and eruption during preadolescent and adolescent growth.[8] Ectopic eruption of the maxillary permanent first molars, which occurs in about half of individuals, causes premature loss of the deciduous second molars and mesial drifting of the molars.[8] Often, a second premolar will erupt palatally, contributing to further impaction and crowding. Unilateral and bilateral posterior crossbites are prevalent in two thirds of affected persons. These individuals experience high caries risks due to lack of motivation and mobility restrictions from fused shoulder and elbow joints, and hand anomalies, making it difficult to maintain adequate oral hygiene.[7,9]

The purpose of this study was to evaluate the final treatment outcomes of the team care provided for individuals with Apert syndrome.

MATERIAL AND METHODS

This was a retrospective study conducted with records from the University of California at San Francisco's Center for Craniofacial Anomalies Filemaker database by using the keywords "Apert syndrome" and "craniosynostosis." There were 46 subjects in the initial sample. Of these,

Table III. Cephalometric measurement comparisons between Apert individuals at the 2 time points

Measurement	*T1*	*T2*	P *value*
Cranial base measurements			
Anterior cranial base (SN) (mm)	64.8	66.9	0.139
Sagittal maxillary measurements			
SNA (°)	71.6	82.3	0.002*
Maxillary length (Co-ANS) (mm)	63.8	73.4	0.001*
Sagittal mandibular measurements			
SNB (°)	85.1	82.9	0.274
Mandibular length (Co-Pg)	103	104	0.268
Sagittal jaw relationships			
ANB (°)	−13.5	−0.613	0.004*
Wits appraisal (mm)	−12.0	−4.76	0.003*
Vertical maxillary and mandibular measurements			
FMA (MP-FH) (°)	25. 3	30.8	0.009*
Lower face height (ANS-Me) (mm)	70.1	71.6	0.241
Upper incisor-palatal plane (°)	43.5	32.1	0.030*
Dentoalveolar measurements			
U1-NA (°)	43.5	32.1	0.030*
U1-NA (mm)	17.4	10.9	0.021*
L1 protrusion (L1-APo) (mm)	8.86	3.74	0.001*
L1-NB (mm)	4.48	4.81	0.654
Interincisal angle (U1-L1) (°)	125	123	0.378
Soft-tissue measurements			
Upper lip to E-plane (mm)	−9.80	−6.20	0.0001*
Lower lip to E-plane (mm)	−4.16	−4.18	0.992

T1, Before surgery; *T2*, time point furthest from surgery.
*$P < 0.05$.

25 met the inclusion criterion of having had the final midface advancement. Additional inclusion criteria were complete clinical and radiographic records and no previously published articles about these individuals. Eight subjects met these criteria (Table I). Cephalometric films taken before midface advancement and after completion of all treatment were compared.

The lateral cephalograms obtained before 2006 were taken on a cephalostat with magnification of 9.8%. These images were then scanned (U Max Power Look 1100; UMAX Technologies Inc, Dallas, Tex), and the magnification was calibrated to the digital images that were obtained between 2006 and 2010 with no magnification, and stored in Dimaxis Pro (version 3.3.1; Planmeca, Roselle, Ill). Fifty-three hard-tissue and soft-tissue landmarks were digitized by an orthodontist (S.O.) using Dolphin software (version 10.5; Dolphin Imaging and Management Solutions, Canoga Park, Calif). Thirty-five angular and linear measurements were analyzed. The landmarks and measurements are described in Table II.

Statistical analysis

Measurements taken at the 2 time points were compared and tested for statistically significant differences with paired *t* tests. Two-tailed *P* values of less than or equal to 0.05 were reported as statistically significant.

Lin's concordance was used to assess intrarater reliability of the orthodontist's duplicate measurements. Five randomly selected cephalograms were traced twice 3 weeks later.

RESULTS

Analysis of the digitizing errors produced Lin's concordance values between 0.8 and 0.9 for all intraclass correlation measurements across 35 variables on the repeated measurements, indicating good to excellent intrarater reliability.

Cephalometric measurements and comparisons are shown in Table III. The anterior cranial base length showed no difference between the 2 time points, as expected.

All sagittal maxillary measurements showed significant increases: SNA increased by 10.7° ($P = 0.002$) and maxillary unit length by 9.6 mm ($P = 0.001$). The sagittal mandibular measurements showed no significant difference between the 2 time points because most mandibular growth was completed at the age of midface advancement.

Sagittal jaw relationship measurements including ANB changed by 13.1° ($P = 0.004$) and the Wits appraisal

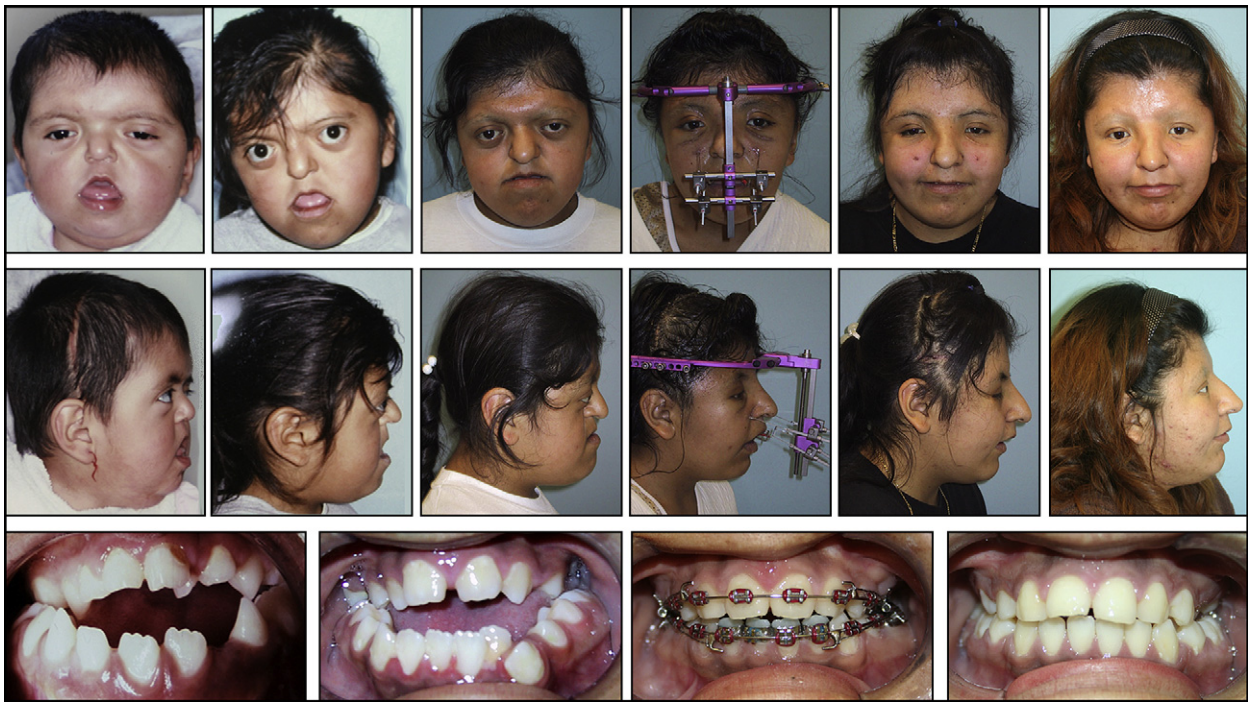

Fig. Facial morphology and occlusal changes from early childhood through surgical and orthodontic treatment to adulthood in a patient with Apert syndrome.

by 7 mm ($P = 0.003$). Vertical change was shown as a significant increase in the mandibular plane angle of 6° ($P = 0.009$). The only significant dentoalveolar change was mandibular incisor inclination: protrusion increased by 5.1° ($P = 0.001$); this would be associated with the significant change in the mandibular plane angle.

The only significant soft-tissue change was the upper lip to E-plane, which changed by 3.6° ($P = 0.001$).

DISCUSSION

There are differing opinions on the best timing of surgical advancement for midface hypoplasia. Obstructive sleep apnea or severe exorbitism are absolute indications for early midface advancement according to Posnick et al.[10] Otherwise, the procedure can be performed in children aged 5 to 8 years or postponed until skeletal maturity. The University of California at San Francisco craniofacial team prefers to advance the midface during the 9 to 12-year age range if functional demands have not dictated earlier intervention. The rationale for that timing is that, at that age, the midface can be advanced enough for the adult face, and the procedure does not need to be repeated later. From age 9, there is minimal forward growth at orbitale in the general population.[11] It is well established that the midface remains stable after advancement, whether by distraction or standard LeFort III procedure. However, it does not grow forward after surgical advancement.[12-14] When done before growth completion, the additional mandibular growth can be compensated for by orthodontic treatment and a LeFort I advancement. In this study, the average age at advancement was 15 years, so most of the growth was completed, and repeated midface advancement was not required.

In this study, we focused on assessing the treatment outcomes of 8 individuals who had standard LeFort III advancement or distraction. Both groups were small and were combined for the analyses. When comparing the measurements before the surgical intervention with those at the second time point furthest from the distraction or advancement, there was no significant change in the anterior cranial base. This was expected, since the surgical intervention involved the midface only.

There was a 10.7° increase in the SNA angle, and the midface length increased by 9.6 mm. SNB moved backward by 2.2° by the clockwise rotation resulting from midface lengthening. The amount of midface advancement and the normalization of facial proportions were comparable with the results of other studies.[12-16]

A main limitation of this study was the small sample size. This was in part due to the low incidence of Apert syndrome, variations in timing of interventions because of patient compliance and delayed dental eruption, and

Table IV. Summary of subject characteristics and team interventions

Subject	Sex	Cleft palate	Palate surgery	Speech status	Forehead advancement	Shunt placement
1	M	CP	+	VPI, oral distortions on sibilants, gliding	+	–
2	F	SMC	–	Interdentalizations and lateralizations, vocal quality hoarse and breathy	+	+
3	F	SMC	+	95% intelligible speech, gliding of /r/, denasal	+	–
4	F	–	–	Normal speech	+	
5	F	CP	–	85% intelligible interdental fricatives and gliding of /r/	+	+
6	F	SMC	–	85% intelligible interdental fricatives and gliding of /r/	+	+
7	F	CP	+	80% intelligibility	+	+
8	M	–	–	70%-80% intelligibility	+	+

CP, Cleft palate; *ENT*, ear, nose, and throat; *F*, female; *M*, male; *PE*, pressure equalization tubes; *RED*, rigid external distraction; *SMC*, submucous cleft palate; *T&A*, tonsillectomy and adenoidectomy; *VPI*, velopharyngeal insufficiency; +, received treatment; –, did not receive treatment.

incomplete records at specific times. These limitations are commonly associated with retrospective studies.

The following summarizes the University of California at San Francisco team's protocol for craniosynostosis syndromes.

1. Immediately after birth: counseling; feeding instructions; team evaluation including genetics, neurosurgery, orthopedics, pulmonology, audiology, and ear, nose, and throat evaluations; imaging as needed; shunt placement; and tracheostomy if indicated.
2. Six to 12 months: fronto-orbital advancement by a team of craniofacial and neurosurgeons; address the syndactyly.
3. One to 2 years: team visits to address skull and cognitive development, speech and language development, dental and oral hygiene issues; and determine the timing of cleft palate repair if a cleft is present.
4. Two to 7 years: team visits; medical and behavioral intervention as needed (speech therapy, treatment for middle ear disease, and so on); monitor dental development and eruption, and jaw and facial growth; radiographs or computed tomography scans at intervals as needed.
5. Seven to 9 years: team visits, orthodontic records, dental extractions, and phase 1 orthodontic treatment with maxillary expansion in preparation for midface advancement.
6. Nine to 12 years: team visits, midface advancement by standard LeFort III with bone grafts or rigid external distraction, which is preferred if the individual's cooperation allows.
7. Twelve to 21 years: team visits, orthodontic records, phase 2 orthodontic treatment in preparation for orthognathic surgery after growth completion as needed, complete postsurgical orthodontic treatment and long-term orthodontic retention with final records, forehead contouring, nose revision, and genioplasty if indicated.

All team visits include evaluations by core team members (Table IV). A patient representing team care from infancy to adulthood is shown in the Figure.

CONCLUSIONS

Management of individuals with Apert syndrome requires a team of experienced specialists and extends over the entire growth period from infancy to adulthood. Both standard LeFort III and distraction techniques are effective surgical interventions for treatment of the midface hypoplasia. Significant anteroposterior and vertical correction of the midface is achieved and the severity of the deformity greatly reduced, although it is rarely completely corrected. When the management protocol is followed, long-term improvements of the physical features and functions such as breathing, mastication, oral health, and health of the eyes are achieved. We extrapolate that this also leads to improved psychosocial well-being.

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Table IV. Continued

Hand surgery	*ENT surgery PE tubes/T&A*	*Phase 1 treatment*	*Midface advancement surgery*	*Phase 2 treatment*	*LeFort I advancement*	*Septorhinoplasty*
+	+/+	+	LeFort III/RED	+	–	–
+	+/+	+	LeFort III/I	+	–	+
+	+/–	+	–	+	+	–
+		+	LeFort III	+		–
+	+/+	+	LeFort III/RED	+	+	+
+	+/+	+	LeFort III/RED	+	–	+
+	+/+	+	LeFort III	+	+	+
+	+/+	+	LeFort III	+	–	+

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