Apert Syndrome Management: Changing Treatment Algorithm

Cassio Eduardo Raposo-Amaral, MD, PhD, Rafael Denadai, MD,* Yuri Moresco de Oliveira, MD,* Enrico Ghizoni, MD, PhD,*† and Cesar Augusto Raposo-Amaral, MD**

Background: The purpose of this study is to review 10 years of surgical experience in the management of Apert syndrome, focusing on an updated algorithm which includes hand reconstruction and posterior vault distraction osteogenesis (PVDO). Additionally, the authors compare PVDO, which is currently used, with fronto-orbital advancement (FOA), which was utilized in a previous algorithm.

Methods: An observational retrospective study was performed on consecutive patients with Apert syndrome who underwent upper and lower limb reconstruction and craniofacial surgery between 2007 and 2017. A modified Clavien–Dindo surgical complication scale was used to stratify complications between PVDO and FOA. Demographic, surgical, and outcome data was also recorded. The blood transfusion rate between PVDO and FOA was also assessed and compared utilizing the Student *t* test.

Results: The present study included 69 patients with Apert syndrome (34 males and 35 females). Craniofacial surgeries were performed on a total of 38 patients. A total of 210 operations were performed on the respective upper and lower limbs of patients included in this study. A total of 18 patients underwent PVDO (n = 9) and FOA (n = 9). Posterior vault distraction osteogenesis required significantly less transfused blood volume than FOA ($P < 0.05$). Complication rate and length of hospital stay were similar for each procedure.

Conclusion: An updated algorithm to treat Apert patients was implemented. Posterior vault distraction osteogenesis incorporated into an updated algorithm results in a lower blood transfusion rate.

Key Words: Apert syndrome, craniofacial dysostoses, syndromic craniosynostosis, craniosynostosis, acrocephalosyndactyly

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From the *Institute of Plastic and Craniofacial Surgery, SOBRAPAR Hospital, Campinas; and †Department of Neurology, University of Campinas (UNICAMP), São Paulo, Brazil.

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Address correspondence and reprint requests to Cassio Eduardo Raposo-Amaral, MD, PhD, Institute of Plastic and Craniofacial Surgery, SOBRAPAR Hospital, Av. Adolpho Lutz, 100, Caixa Postal: 6028, Campinas, São Paulo 13084-880, Brazil;
E-mail: cassioraposo@hotmail.com

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Among the many significant advances achieved in craniofacial surgery within the past decade, 1 specific technique, posterior vault distraction osteogenesis (PVDO), has resulted in modified algorithms for the treatment of Apert syndrome. Posterior vault distraction osteogenesis represents a major paradigm shift in the treatment of craniofacial dysostosis.[1,2] Recent studies have demonstrated that PVDO consistently results in increased intracranial volume expansion.[2–4] Whenever possible, our Hospital performs PVDO before a patient reaches 12 months of age. Beginning in 2012, our Hospital replaced standard fronto-orbital advancement (FOA) with PVDO. In addition to craniofacial reconstruction, our Apert treatment algorithm also prioritizes early surgical treatment of Apert hands, enabling children to pinch and grasp objects at a younger age, and also gain manual dexterity.[4–6] Our surgical regimen for Apert hand reconstruction results in 5-digit hands for all patients with Upton type I and II hands.[4] A recent study of Apert patients who completed a specific digit separation surgical regimen has shown that these patients are able to gain similar levels of hand function regardless of Upton hand type.[7]

This study represents our surgical experience in the management of Apert syndrome, focusing on a recently developed algorithm that added a 5 digit-separation surgical regimen for hand reconstruction and PVDO. Additionally, we compare transfusion rate, complication rate, and length of hospital stay between PVDO and FOA; 2 procedures that are performed as part of 2 separate algorithms.

PATIENTS AND METHODS

A retrospective study was conducted on consecutive patients diagnosed by our multidisciplinary craniofacial team as having Apert syndrome, who underwent surgery between 2007 and 2017. Patients with incomplete medical records, and those who underwent monobloc advancement or immediate subcranial Le Fort III, without distraction osteogenesis, were excluded from this study.

Demographic data (gender and age at surgery), surgical data, and outcome data (perioperative and long-term complications) was verified via medical records, clinical photographs, radiographic images, and interviews with all included patients and/or their parents. Complications were stratified based on a modified Clavien–Dindo surgical complication scale.[8] Complications that merely required pharmacologic treatment or intervention without the necessity of hospitalization were recorded as minor. Major complications were substratified into I, II, and III; (I) events requiring initial or subsequent intervention with general anesthesia to address the resulting condition, (II) events with permanent sequelae, and (III), events resulting in fatality (Supplemental Digital Content, Table 1, http://links.lww.com/SCS/B22).

All subjects were enrolled after parental and patient consents were obtained, and the study was performed in accordance with the Helsinki Declaration of 1975, as amended in 1983. Local institutional research ethics board approval was obtained for this study.

Prior Algorithm (2007–2011)

Apert patients were initially evaluated in our Hospital by a multidisciplinary team. Treatment priorities were determined on an individual basis, based on severity of the patient's condition. Primary attention was given to airway management and corneal exposure caused by severe proptosis. Assessments of breathing obstruction at multiple levels were made, and appropriate procedures were performed as needed. Tracheostomy and tarsorrhaphy if indicated were performed. The neurological status of the patient determined the timing of the first craniofacial operation. If warranted by the patient's condition, Apert patients with cloverleaf deformity underwent decompressive surgery to treat intracranial hypertension, which was performed prior to other craniofacial procedures. If there was no urgency, craniofacial surgery was performed at 6 months of age. Fronto-orbital advancement was performed using immediate movement, and fixation was done with wires. After airway status evaluation, palate repair was performed at 2 years of age. Our craniofacial team always includes a periodontist who guides and counsels patient families on how to comprehensively support their children in oral and dental hygiene matters.

When an Apert patient reached 7 years of age, our Hospital performed a comprehensive assessment which included fundoscopy, an ophthalmological exam for visual acuity, a sleep apnea screen, a nasal endoscopy, and a dental evaluation. We also provided both orthodontic and psychological treatment. For patients between 7 and 9 years of age, either monobloc advancement or subcranial Le Fort III was performed, depending on the projection of the forehead and the patient's overall condition. Monobloc advancement with facial bipartition using distraction osteogenesis was performed whenever hypertelorism was moderate or severe. At 9 years of age, the metacarpal bone union was released, followed by treatment of any radial thumb and index finger deviation.

At 13 years of age, a split calvarial bone graft was added to the nose to create nasal elongation and dorsum augmentation. If relapse occurred in the orbital zygomatic region, either a subcranial Le Fort III or a Le Fort II was performed when the patient was between 17 and 18 years of age. Alternatively, if the bony structures at the orbital zygomatic level did not demonstrate that relapse had occurred, orthognathic surgery was performed after skeletal maturity to ameliorate any remaining malocclusion.

Once the patient reached 18 years of age, final bony and soft tissue refinements such as lateral and medial canthopexies and fat grafting were performed as needed. Neurological, ophthalmologic, and otorhinolaryngologic procedures were performed during the treatment algorithm as needed.

Current Algorithm (2012-Present)

The current algorithm in our Hospital for procedures of this type is similar to the previous algorithm described above, but there are some important differences.

Unless the Apert patient presents a cloverleaf type of craniosynostosis, we begin the first stage of hand reconstruction at 4 months of age. If the Apert patient has a cloverleaf type of craniosynostosis, decompressive craniectomies are performed at 3 months of age or earlier, as these patients have high intracranial pressure, accompanied by insufficient skull thickness, and multiple bone defects representing incomplete ossification of the cranial vault. After intracranial pressure is released, there is rapid brain expansion followed by osteogenesis at the posterior region and mid cranial vault, which can be subsequently treated by PVDO.

After the first stage of hand reconstruction has been completed, a radiologic evaluation (magnetic resonance imaging or computed tomography venogram) is performed to detect stenosis of the superior sagittal sinus, and the presence of important supra-tentorial collateral emissary veins (CEV). The presence of supra-tentorial CEV can preclude performance of the PVDO procedure due to the severe risk of unmanageable intracranial hypertension if those CEV are ligated.[9,10] In the absence of important supra-tentorial CEV at craniotomy site, PVDO is performed at 6 months of age. It is noteworthy that venous hypertension due to stenosis of the transverse or sigmoid sinuses does not rule out PVDO. Fronto-orbital advancement is reserved solely for those patients with stenosis of the superior sagittal sinus and any evidence of CEV drainage dependence.

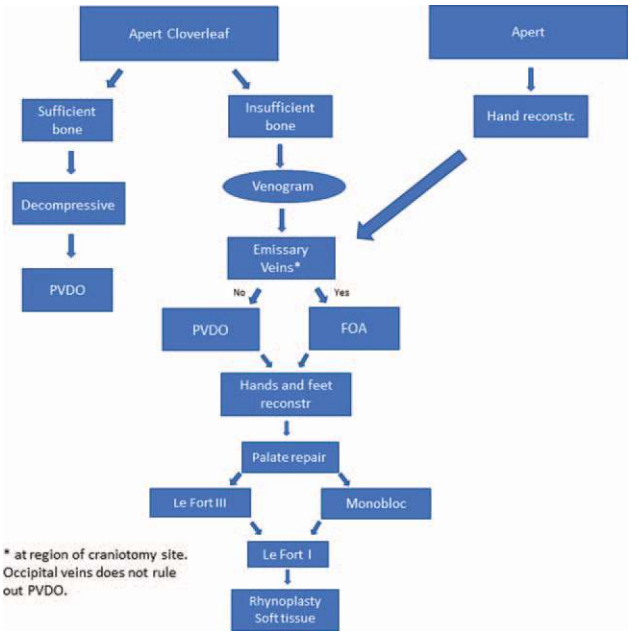

FIGURE 1. Apert syndrome algorithm.

Our hand reconstruction regimen is then finalized according to Upton hand type, and a lower limb digit separation regimen is initiated.

With regard to midface advancement, monobloc advancement with facial bipartition remains the procedure of choice, and Le Fort III is indicated for any syndromic patient who has a projected forehead as a result of previous successful FOA.

The preferred technique for midface advancement is monobloc bipartition using distraction osteogenesis, which enables orbital mobilization, and soft tissue reconfiguration by rotating the lateral palpebral fissures. Subsequent procedures to treat additional digit deviation, midface and nose deformities, and soft tissue refinements,[11,12] are performed in the same manner as previously described above in our prior algorithm. Fat grafting using principle-based methods and fat compartment theory is performed as needed[13,14] (Fig. 1).

Statistical Analysis

For the descriptive analysis, the mean was used for metric variables, and percentages were given for categorical variables. The chosen variables used for comparison between PVDO and FOA were blood volume per kilogram transfused, type of complication, and length of hospital stay, using the Student *t* test. All analyses were performed using IBM SPSS Version 20.0 (IBM Corp, Armonk, NY). Values of $P \leq 0.05$ were deemed to be statistically significant.

RESULTS

The present study included 69 patients with Apert syndrome (34 males and 35 females). Craniofacial surgeries were performed on a total of 38 patients. A total of 210 operations were performed on the respective upper and lower limbs of the patients included in this study. Upper and lower limb reconstruction (n = 210) was performed solely by the same specific surgeon (CER-A), and craniofacial surgeries were performed by the same craniofacial surgeon (CER-A), and neurosurgeon (EG), between 2007 and 2017 (Supplemental Digital Content, Table 2, http://links.lww.com/SCS/B22). With regard to upper limbs, affected hands were stratified according to Upton classification for hand severity into type I (40%), type II (21.66%), and type III (38.33%), and a specific reconstruction regimen was designed for each patient, depending on age at presentation (Supplemental Digital Content, Table 3, http://links.lww.com/SCS/B22).

Craniofacial surgeries were performed in 38 patients. Procedures were stratified into decompressive surgery, PVDO, FOA, Le Fort III, and monobloc distraction, with or without facial bipartition (Supplemental Digital Content, Table 4, http://links.lww.com/SCS/B22). PVDO and FOA were performed on 9 patients each, totaling 18 procedures. The blood transfusion rate in patients who underwent PVDO was lower than those who underwent FOA ($P < 0.05$). Complication rate and length of hospital stay were similar between PVDO and FOA (Figs. 2–4).

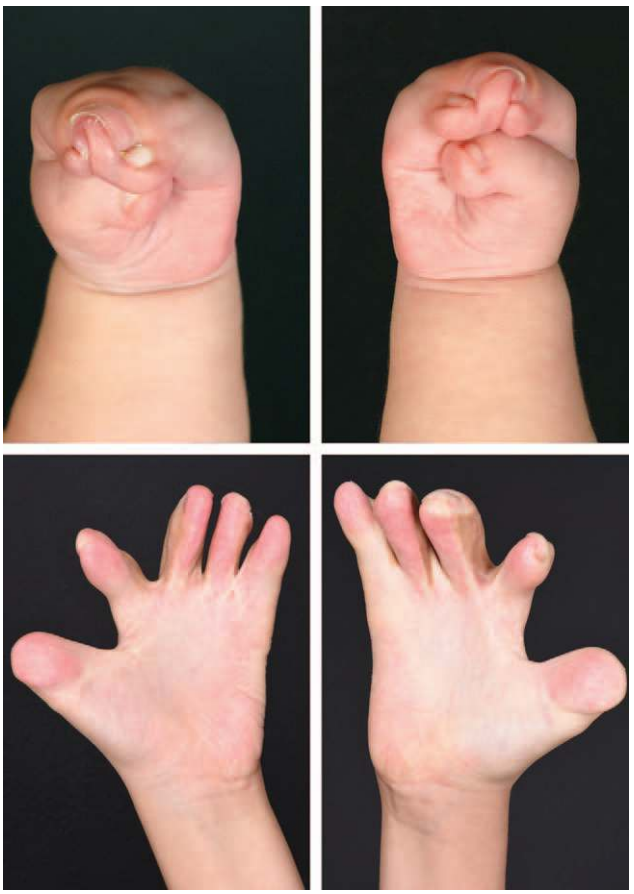

FIGURE 2. (Left) Preoperative view of a 4-mo-old patient with Apert hands. (Right) postoperative view of the same patient after 8 y of follow-up care subsequent to completion of a 5-digit hand separation regimen.

FIGURE 3. (Left) Preoperative lateral view of a 6-mo-old Apert patient who underwent posterior vault distraction osteogenesis. (Center) Postoperative lateral view of the same patient 4 mo after distractor removal, and after 2 y of follow-up care (right).

DISCUSSION

Taylor and Bartlett[15] noted a wide range of clinical presentation for syndromic craniosynostosis, and the need for an individualized and tailored approach in treating each specific type of deformity. In our Hospital, we have seen that the severity of a patient's craniofacial deformity does not directly correlate with the severity of a patient's hand deformity, despite the fact that all of our patients with cloverleaf deformity (the most severe craniofacial phenotype) also presented Upton type III hands.

In Apert patients with cloverleaf deformity and hydrocephalus accompanied by high intracranial pressure, a VP shunt enables modification of the ossification pattern, resulting in increased bone growth, and effectively addresses a life-threatening condition. However, a VP shunt should only be placed if hydrocephalus is the main cause of intracranial hypertension so as to not jeopardize the brain's expansion capability, which is responsible for both vascularizing the frontal bone flaps and preventing dead space. For these particular cloverleaf patients, decompressive surgery alleviates excessive intracranial pressure and modifies the ossification pattern, so that PVDO can subsequently be performed.

Whenever possible (ie, in the absence of cloverleaf deformity, and in Apert patients referred to our Hospital at an early age), hand

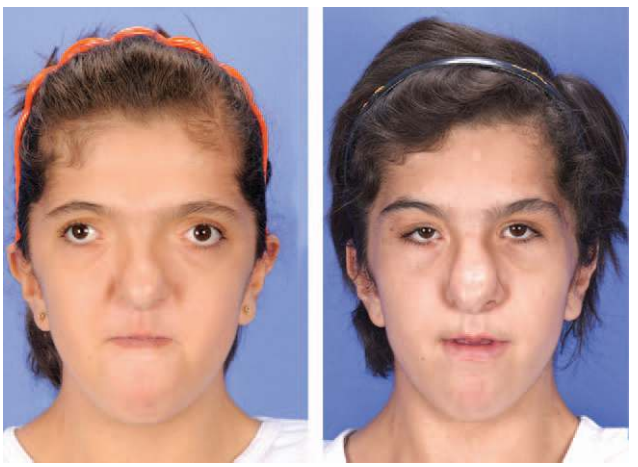

FIGURE 4. (Left) Preoperative lateral view of an 11-y-old Apert patient who underwent monobloc advancement with facial bipartition. (Right) Postoperative lateral view of the same patient 1 y after surgery. Note that the treatment of hypertelorism by medialization of the orbits enabled rotation of the palpebral fissures, and reduced some of the characteristics of the Apert face. As the patient's divergent strabismus was corrected by medialization of the orbits, no additional ophthalmological surgery was required.

reconstruction is initiated when the patient is 4 months old, prior to any craniofacial surgery.

As our Hospital receives patients from all over the country,[16] approximately 70% of our patients are not seen until after the optimal age for early surgery has already passed.[17] Thus, we often need to delay operating on an Apert patient's hands until we have first addressed all craniofacial issues. The rationale for starting hand reconstruction as early as possible is that we have anecdotally observed less growth disturbance and secondary deviation of the index finger in younger patients, when compared with those patients who are operated on subsequent to reaching 12 months of age. Following syndactyly separation of the 4 and 5 fingers as per our treatment algorithm, patients were able to manipulate shirt and/or blouse buttons, pinch and grasp numerous small objects, feed themselves using standard cutlery items such as forks, knives, and spoons, operate a cell phone and/or tablet, open and close zippers, write and draw using pencils and pens, open envelopes, connect and disassemble Lego pieces, put on and take off velcro strapped sandals, use scissors, uncap and cap toothpaste tubes, brush their teeth, put on and remove eyeglasses, open and close car doors, open and close water faucet taps, and some patients were even able to play individual notes on a musical keyboard.

Posterior vault distraction osteogenesis is utilized as a first-line surgical procedure for all of our Apert patients, as it ensures that pristine tissue will be available when the monobloc distraction procedure is subsequently performed. As the presence of CEV under the skin at the posterior region may compromise indications for PVDO,[18] our Hospital always performs an magnetic resonance imaging or computed tomography venogram at the beginning of our standard treatment algorithm. Patients who undergo posterior advancement always present increased cranial volume postdistraction, and consequently less frontal contour irregularities and turricephalies,[19] enabling us to delay midface advancement until a patient reaches 9 years of age. Additionally, our data has demonstrated a lower transfusion rate using PVDO in comparison with FOA.

The percentage of patients among the various reported studies who experienced complications due to PVDO was as high as 100%, with cerebrospinal fluid (CSF) leakage being the most prevalent complication.[20] Other complications resulting from PVDO have also been described, such as failure of the distraction process, and wound dehiscence followed by distraction footplate exposure.[21,22]

In our study, 1 Apert patient with a cloverleaf deformity who underwent PVDO instead of decompressive surgery experienced a major complication. This complication occurred when PVDO was first utilized to treat a syndromic patient with severe cloverleaf deformity as an alternative to decompressive surgery. However, the majority of patients having this deformity lack sufficient bone density, thereby precluding stable fixation of the distractor footplates. Additionally, minor dural tears sustained during distractor placement will not heal if either high venous or CSF hypertension is present.

All Apert patients at our hospital who had CSF leakage presented cloverleaf deformities. As stated by Greives et al,[20] there is a learning curve for all new procedures, and it is important to develop both effective maneuvers and appropriate algorithms to select the best candidates for these procedures. In light of this, we designed a specific algorithm to define priorities in the management of upper and lower limb and craniofacial reconstruction.

As standard practice, our Hospital performs fronto-facial monobloc advancement with facial bipartition and distraction osteogenesis. This technique enables medialization of the orbits, alleviates downslanting of the palpebral fissures, and corrects divergent strabismus, which are common features of the Apert face.[11] As the majority of Apert patients also have hypertelorism, monobloc advancement with facial bipartition enables medialization of the orbits, and destigmatization of the Apert face.[23]

As indicated by breathing status, patients may still require turbinectomies and tonsillectomies, even after palate repair at 2 years of age; the performance of which enables postponement of the first midface advancement until the majority of skeletal growth has been achieved between ages 7 and 9. Early monobloc advancement is not indicated, even in patients with severe breathing issues. In these cases, a tracheostomy is performed.

Our study is not without limitation. The longitudinal beneficial effect of our updated algorithm has not been evaluated, as these patients upon whom we performed PVDO have not yet reached skeletal maturity. Although we have a significant number of Apert patients being followed at our Institution (n = 69), 20 patients had their first craniofacial operation done elsewhere, and were initially referred to our Hospital for upper and lower limb reconstruction. Among those patients who had their craniofacial surgeries done elsewhere, it is noteworthy that none of them underwent PVDO. Fronto-orbital advancement is still the procedure of choice in Brazil.

Despite these caveats, the present study is one of the largest studies involving Apert patients in the literature, and incorporates both early hand reconstruction and PVDO into a treatment algorithm.

CONCLUSION

Posterior vault distraction osteogenesis had a lower blood transfusion rate than FOA. Complication rate and hospital stay were similar between the 2 procedures. Early hand reconstruction and PVDO were included into the updated algorithm.

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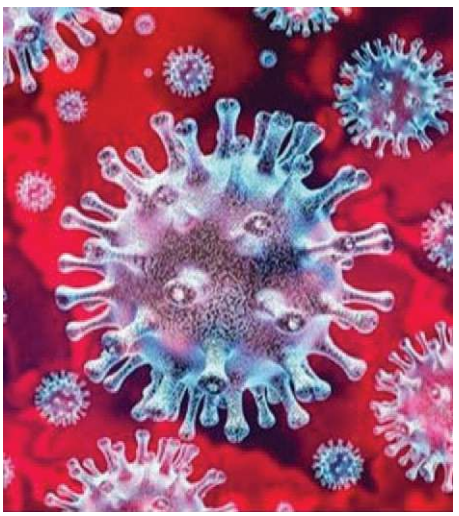

The invisible enemy.