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SPECIAL TOPIC
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Crouzon Syndrome Spanning Three Generations: Advances in the Treatment of Syndromic Midface Deficiency

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Background: Crouzon syndrome is an autosomal dominant genetic disorder characterized by craniosynostosis, midface retrusion, and exophthalmos. Over the past century, the treatment of craniofacial disorders like Crouzon syndrome has evolved significantly.

Methods: An institutional review board–approved retrospective study was conducted to ascertain the treatment of three individuals with Crouzon syndrome from one family, complemented with a series of literature searches to examine the evolution of craniofacial surgical history.

Results: Dr. David Williams Cheever developed the Le Fort I level to correct malocclusion, maxillomandibular malformations, and midface hypoplasia. Later, Dr. Paul Tessier introduced the Le Fort II and III osteotomies to treat syndromic midface hypoplasia. In 1978, Dr. Fernando Ortiz-Monasterio and Dr. Antonio Fuente del Campo published the first series of monobloc osteotomies, allowing for simultaneous correction of supraorbital and midface malformations, although complicated by blood loss and high infection rates. In 1992, McCarthy et al introduced the concept of gradual distraction to the craniofacial skeleton. In 1995, Polley et al performed the first monobloc advancement using external distraction. Subsequently, in 1997, Polley and Figueroa introduced a rigid external distraction device with multiple vector control to manage severe cleft maxillary hypoplasia. The technique was further refined and applied to treat syndromic midface hypoplasia, reducing complication rates. Currently, either external or internal distraction approaches are used to safely treat this challenging group of patients.

Conclusion: The treatment of syndromic midface deficiency has significantly evolved over the past 50 years, as evidenced by this report of three generations of Crouzon syndrome. *(Plast Reconstr Surg Glob Open 2023; 11:e5296; doi: 10.1097/GOX.0000000000005296; Published online 28 November 2023.)*

INTRODUCTION

Craniosynostosis is defined as the premature fusion of one or more cranial sutures. Syndromic craniosynostoses are estimated to account for 15% of all craniosynostoses, with 8% being familial or inherited.[1] Crouzon syndrome is the most common, with 16.5 cases per million live births and a prevalence of one in 60,000 in the United States.[2,3] It is hypothesized to arise from mutations in the *FGFR2* and *FGFR3* genes on chromosome 10 and is inherited in an autosomal dominant pattern.[4,5] The syndrome was first reported in 1912 by French neurologist Octave Crouzon, who described a 29-year-old woman with prognathism, maxillary hypoplasia, diverging strabismus, and exophthalmos. The author also described it in the patient's 3-year-old son with a similar facial appearance, bilateral exophthalmia, strabismus, and papilledema.[6]

The premature cranial suture fusion and abnormal bone growth found in Crouzon syndrome can result in several craniofacial malformations, such as plagiocephaly, brachycephaly, turricephaly, and cloverleaf skull.[7] Due to involvement of the cranial base and midface sutures, patients with syndromic craniosynostosis often present with midface

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hypoplasia, resulting in a high-arched palate, dental crowding, maxillary retrusion, reduced nasal length, and exorbitism.[8] Other physical manifestations of Crouzon syndrome include frontal bone abnormalities, hypertelorism, frontal bossing, shallow orbits with proptosis, maxillary hypoplasia, abnormal mandibular shape, class III malocclusion, and cervical spinal fusions (30%).[7,9,10]

Crouzon patients usually have normal extremities and preservation of mental capacity. However, if left untreated, the premature fusion of the cranial sutures may result in persistently increased intracranial pressure (ICP), leading to papilledema, optic nerve compression, and potentially, blindness and intellectual disability.[9] In addition, these patients commonly present with breathing difficulties secondary to the severe midface deficiency and narrowing of the nasopharyngeal and oropharyngeal airways.[11]

Management of Crouzon syndrome includes addressing suture synostosis by cranial release and correction of midface deficiency, proptosis, airway narrowing, and malocclusion with midface skeletal advancement. Cranioplasty is typically performed at 3–6 months of age with frontal orbital advancement.[7] Early intervention is crucial in reducing the potential sequelae of elevated ICP by improving cerebral blood flow and abnormal morphology of the skull, orbits, and upper jaw.[12] Optimizing the timing and method of initial intervention have proven to be key to providing the best outcome while minimizing the total number of operations required long-term.[13]

Midface advancement may also be indicated in cases with concern for vision impairment, obstructive sleep apnea (OSA), malocclusion, or appearance. The timing of midface surgery is case dependent. It is based on function and, if possible, delayed until the orbits mature between 5 and 8 years of age.[13] Correction of midface hypoplasia has been achieved through osteotomies with fixation or distraction osteogenesis.[14,15] Distraction osteogenesis is often preferred over traditional LeFort III or monobloc advancements due to decreased operative time, blood loss, relapse rate, and need for bone grafting.[7,15] Advancement of the midface decreases ocular exposure and improves OSA and dental malocclusion. While fronto-orbital advancement and Le Fort osteotomies are accepted as early interventions, orthognathic surgery (OGS) for dentofacial abnormalities is typically reserved for the skeletally mature.[16]

Traditionally, Le Fort III and monobloc advancement are applied to correct deformities of the zygoma, orbit, and nasal areas. However, additional OGS is often required, and skeletally mature patients may undergo a combination of the Le Fort III with Le Fort I osteotomies.[17,18] Of note, the ideal timing of surgical intervention for class III malocclusion remains controversial. Some suggest that early treatment may reduce the need for later OGS, whereas others advise against correction in growing patients due to the risk for reoperation as a result of late mandibular growth.[19–24]

Virtual surgical planning has emerged as a useful tool in craniofacial surgery. By creating a three-dimensional virtual model, the technology allows for presurgical determination of osteotomy lines, monobloc design, and the positioning of distraction devices.[25] This presurgical plan can then be translated to aid in the operating room through custom cutting guides, surgical splints, and fixation devices, resulting in improved postoperative outcomes.[26]

In this case study, we review the evolution of treatment of a family with Crouzon syndrome spanning three generations, treated by three generations of craniofacial surgeons.

Takeaways

Question: How has the treatment of syndromic midface deficiency evolved?

Findings: This report describes the treatment of Crouzon syndrome spanning three generations of one family, each treated by a different craniofacial surgeon (Fernando Ortiz-Monasterio, John Polley, and Christina Tragos). Although the monobloc procedure permitted concurrent orbital and midfacial advancement, it was limited by the high rate of infectious complications. Internal and external distraction devices allowed for greater advancement in multiple vectors, while decreasing the complication rate, thus enabling safe usage of the monobloc and facial bipartition procedures once again.

Meaning: To best care for those with syndromic midface deficiency, treatment should be tailored to the individual patient and early intervention should be considered, when appropriate.

RESULTS

Patient 1: Proband

The proband is a 33-year-old woman with a medical history of Crouzon syndrome and scoliosis (Fig. 1). She initially presented to our institution at 16 years old. Her surgical history included traditional monobloc osteotomies

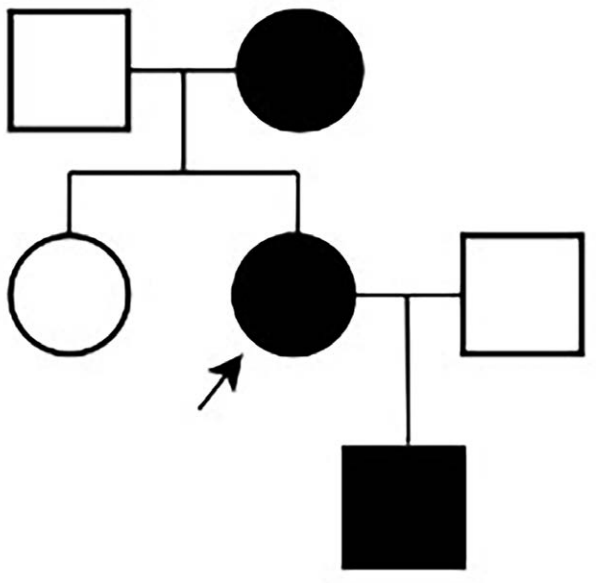

Fig. 1. The pedigree for the family with three generations of Crouzon syndrome. The arrow indicates the proband.

Fig. 2. Frontal (A) and right lateral (B) views of patient 1 (proband) preoperatively. Frontal (C) and right lateral (D) views of patient 1 (proband) postoperatively after traditional monobloc advancement and rigid skeletal fixation. Frontal (E) and right lateral (F) views of patient 1 (proband) postoperatively at 20 years and 10 months of age after Le Fort III, monobloc, and bilateral canthopexies. Frontal (G) and right lateral (H) views of patient 1 (proband) postoperatively at 31 years and 2 months of age after Le Fort I.

with advancement and rigid skeletal fixation performed at 4 years of age by Dr. John Polley, which provided improved eye protection, breathing, and aesthetics (Fig. 2).

Due to recurrence of midface hypoplasia, a deviated septum, and restricted nasal breathing, she underwent fronto-orbital advancement and a LeFort III advancement using a rigid external distraction (RED) device at 16 years of age by Dr. Polley. Her treatment outcome was satisfactory with improvement of nasal breathing, dental occlusion, and appearance. The patient was lost to follow-up for 14 years due to insurance issues.

She returned to our institution at 30 years of age with maxillary hypoplasia, class III skeletal and dental relations, and restricted nasal breathing. She underwent LeFort I osteotomy with maxillary advancement and osseous genioplasty by Dr. Christina Tragos. Due to continued concerns about the appearance of her wide nasal dorsum, ill-defined nasal tip, and protruding brow, she underwent staged nasal reconstruction with a split calvarial bone graft and contouring of the forehead and brow area 4 months later. At 32 years of age, she underwent secondary septo-rhinoplasty with conchal cartilage grafts from the right ear as well as fat transfer for temporal hollowing. Her postoperative course for each of these procedures was unremarkable. At the time of the patient's last follow-up at 2 years postoperatively, she reported satisfaction with her appearance as well as improved oral function and nasal breathing.

Patient 2: Proband's Mother

The proband's mother is a 66-year-old woman with a medical history of Crouzon syndrome with severe features, including exorbitism, midface hypoplasia, and class III malocclusion (Fig. 3). Initially, she was followed up by Dr. Fernando Ortiz-Monasterio in Mexico. There, she underwent traditional monobloc advancement with bone grafts in adolescence.

She later presented to our craniofacial center at 45 years of age with airway stenosis and severe orbital and midface hypoplasia. To address her continued cosmetic and functional issues, she underwent monobloc advancement with an RED device, reconstruction of the left lateral orbit with autologous carved cranial bone graft, and bilateral canthopexies by Dr. Polley. Later that year, she underwent bilateral frontotemporal cranioplasties to improve temporal hollowing. The aforementioned procedures resulted in significant morphological and functional improvement in breathing, eye protection, vision, and mastication.

Patient 3: Proband's Son

The child of the proband is a 13-year-old boy with a medical history of Crouzon syndrome with bilateral exorbitism, left-sided astigmatism, left-sided amblyopia, and bilateral conductive hearing loss with a bone anchored hearing aid (Fig. 4). He initially presented at our institution at 2 years of age. At 2 years and 2 months, he underwent monobloc advancement with an RED device with Dr. Polley to improve exorbitism, breathing, and midface deficiency. Due to a change in the patient's insurance coverage, the mother transferred care to another institution where he underwent a traditional LeFort III osteotomy at age 7.

He returned to our institution at 10 years of age for correction of significantly limited mouth opening secondary to coronoid impingement after the previous LeFort III. His maximum interincisal opening (MIO) was 4 mm, which resulted in decreased food intake and weight loss. At 10 years and 6 months, he underwent bilateral

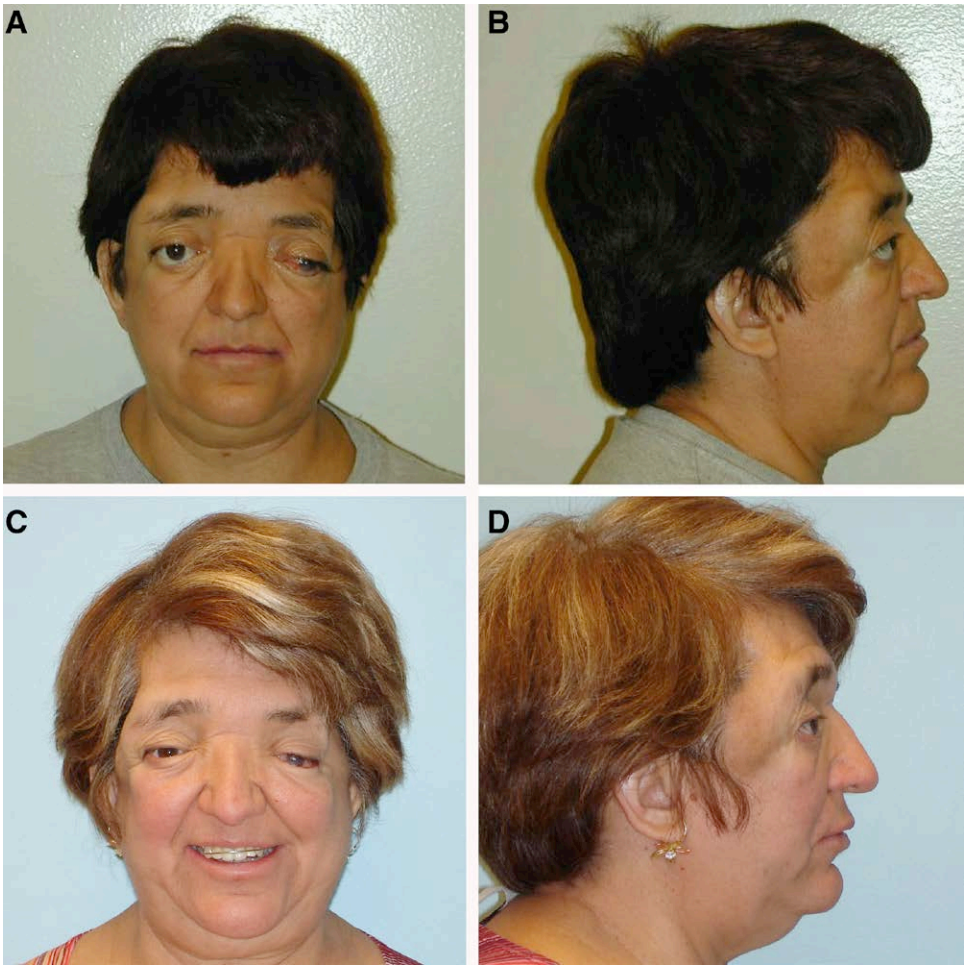

Fig. 3. Frontal (A) and right lateral (B) views of patient 2 (proband's mother) preoperatively at 44 years and 7 months of age (post initial traditional monobloc advancement). Frontal (C) and right lateral (D) views of patient 2 (proband's mother) postoperatively at 52 years and 5 months of age after Le Fort III, monobloc advancement with an RED device, and bilateral canthopexies.

coronoidectomies by Dr. Tragos, resulting in a modest improvement of his MIO to 12 mm. At 12 years and 3 months of age, he underwent LeFort III osteotomies and advancement with an RED device.

To allow for favorable oral function as well as anatomic and psychosocial development, the patient required early orthognathic surgery (OGS). At age 13, he underwent a maxillary LeFort I advancement with bone graft and simultaneous bilateral sagittal split osteotomies of the mandible to correct the maxillary deficiency, open bite, and malocclusion. His postoperative course was uncomplicated. At his most recent follow-up at 14 years of age, his function and occlusion had improved, with an MIO of 30 mm. His mother reported that he was attending school, eating well, and gaining weight. The patient and his mother were made aware that if his growth is unfavorable, he would require additional OGS.

DISCUSSION

Crouzon syndrome is a complex craniofacial condition that involves premature fusion of cranial and facial sutures, resulting in cranial and facial malformations. Early surgical intervention is key to improving craniofacial morphology and function and reducing long-term neurologic, breathing, and ophthalmologic sequelae. In this case study, we report the evolution of surgical techniques in one family with three generations of Crouzon syndrome (Fig. 5).

The two main procedures used to correct syndromic midface hypoplasia include the monobloc and LeFort III osteotomies. Throughout the 1960s and 1970s, Dr. Paul Tessier worked to improve the surgical procedures used to correct craniofacial malformations. He was an early proponent for the use of the LeFort III osteotomy for correction of midface hypoplasia with lower orbital rim involvement, exophthalmos, upper airway obstruction, class III malocclusion, and severe facial aesthetic imbalance.[27] The support of the eye globe relative to the lower orbital rim allowed for lid closure, preventing corneal ulceration, amblyopia, cataracts, and potential vision loss.[28] The LeFort III osteotomies, however, may be complicated by infraorbital nerve injury, globe injury, strabismus, bleeding, and infection.[29]

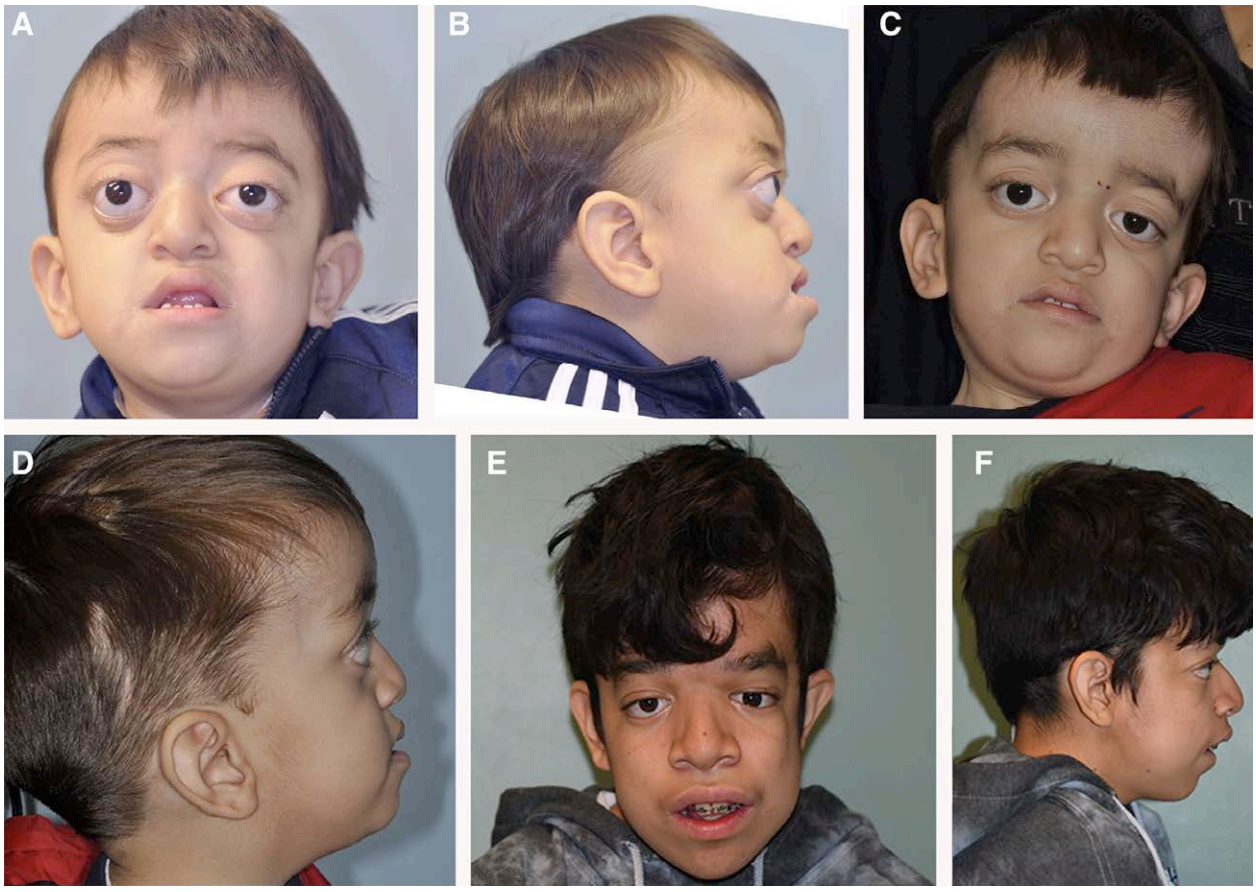

Fig. 4. Frontal (A) and right lateral (B) views of patient 3 (proband's son) preoperatively at 1 year and 10 months of age. Frontal (C) and right lateral (D) views of patient 3 (proband's son) postoperatively at 2 years and 7 months of age after monobloc and Le Fort III advancement with RED device. Frontal (E) and right lateral (F) views of patient 3 (proband's son) postoperatively at 14 years of age after bilateral coronoidectomies, Le Fort III with advancement with RED, and LeFort I.

Fig. 5. All three generations of the family with Crouzon syndrome, including the proband (left), proband's son (middle), and proband's mother (right).

In 1978, Ortiz-Monasterio et al published the first results of a series of patients with Crouzon syndrome treated with monobloc advancement.[30] The monobloc advancement combines the midface advancement achieved by the LeFort III midface advancement with the simultaneous advancement of the lateral and upper orbital rims and frontal bone.[31] The monobloc advancement allows for concurrent correction of midface and supraorbital malformations, thus reducing the number of operations needed and providing a more anatomically correct and natural appearance.[32] However, traditional monobloc advancement was found to be associated with significant blood loss and high rates of complications like infection (>30%; meningitis, epidural abscess, osteomyelitis of frontal bones with bone loss), thought to be caused by the creation of a large nasofrontal space that allowed communication between cranial and nasal cavities.[33] In 1979, van der Meulen modified the monobloc procedure by splitting the facial bone segments, which was further refined by Tessier into the facial bipartition operation.[33] Although surgeons obtained favorable and stable results with the traditional monobloc procedure, the rate of major complications caused surgeons to search for alternatives.

In 1992, McCarthy et al introduced the concept of gradual distraction to the craniofacial skeleton.[34] In 1995, Polley et al performed the first monobloc advancement using external distraction.[35] Subsequently, in 1998, Polley and Figueroa introduced an RED device to manage severe

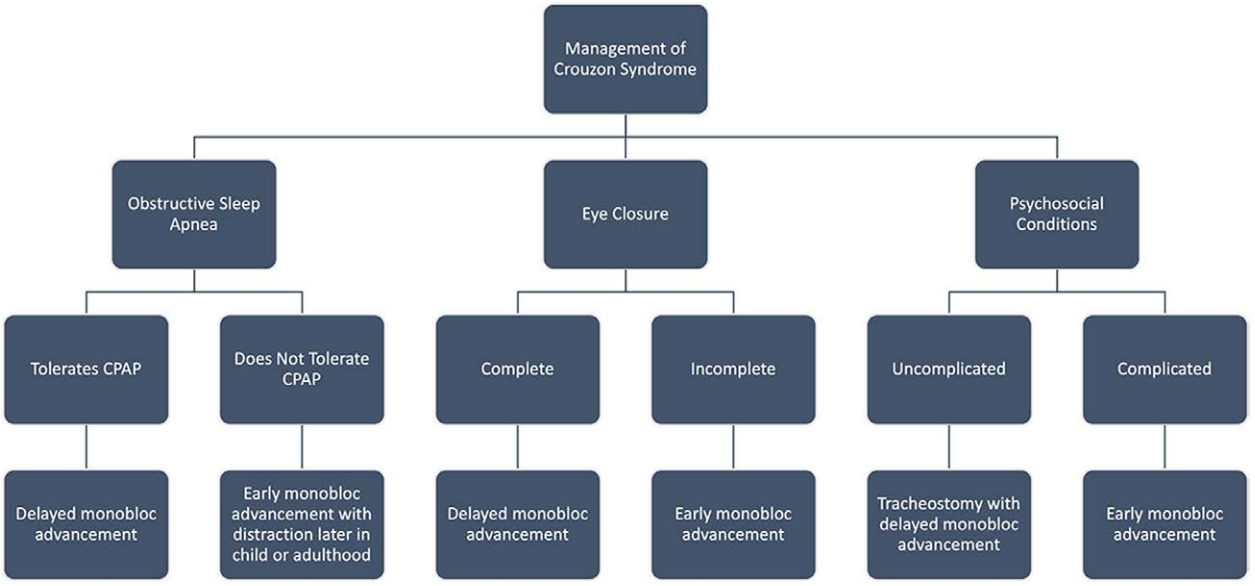

Fig. 6. Algorithm for the treatment of patients with Crouzon syndrome.

cleft maxillary hypoplasia.[36] The technique was further refined and applied to treat syndromic midface hypoplasia.[37,38] With this approach, the complication rate decreased significantly. The RED device is a multivector traction system that allows for controlled adjustments during midface and/or maxillary advancement that are individualized to the patient's needs.[37,39] Gradual osseous distraction causes soft tissue stretching with simultaneous bone generation, allowing for greater midfacial advancement and avoiding the need for bone grafts. If gradual monobloc advancement with RED is used, a nasofrontal space is not created, thus decreasing the risk of infection. Additionally, removal of the device does not require reoperation and can be done in the clinical setting. The RED device, however, is an external device, rendering it susceptible to external forces. With proper parental and patient education, most patients do not have issues. Like any other surgical technique, the operator needs to have adequate training on its use, indications, and contraindications, and it must be performed with the utmost care to avoid potential complications.[40]

Since the introduction of distraction with external or internal devices, the monobloc procedure is once again valuable to those treating patients with craniosynostosis syndromes. The use of the LeFort III osteotomy with an RED technique is also popular as it is a subcranial procedure. Many surgeons will combine these procedures with monobloc advancement in childhood and a finishing LeFort III osteotomy or LeFort II with zygomatic advancement in adolescence, with or without mandibular osteotomies.[41,42] External or internal distraction approaches are currently used to safely treat this challenging group of patients, and surgeons tend to have a preference based on their training, experience, patient response, and outcomes.[43]

In this study, the authors highlight the evolution of surgical techniques used to treat patients with Crouzon syndrome. Although monobloc and LeFort III osteotomies were traditionally used to correct midface hypoplasia, they were associated with significant adverse effects. The introduction of gradual distraction techniques, such as the RED device, revolutionized the treatment of midface deficiency, allowing for surgeons to achieve controlled, individualized adjustments with lower rates of complications. Armed with the surgical techniques available to them, Drs Ortiz-Monasterio, Polley, and Tragos tailored surgical treatment to each patient's unique needs, resulting in improved craniofacial morphology, function, and aesthetic outcomes in the three patients. These cases underscore the importance of early surgical intervention in reducing long-term respiratory, ophthalmological, and neurological adverse outcomes. An algorithm outlining the treatment of Crouzon syndrome complicated by OSA, insufficient eye closure, and complex psychosocial conditions is presented in Figure 6.

This study provides a valuable addition to the literature on the evolution of the treatment of syndromic midface deficiency over time. A different craniofacial surgeon operated on each generation of the presented family (Drs. Fernando Ortiz-Monasterio, John Polley, and Christina Tragos). A unique approach was used based on the existing experience available to each of them during their professional careers.

CONCLUSIONS

The treatment of syndromic midface deficiency has significantly evolved, as evidenced by this report of three generations of Crouzon syndrome in one family treated by three generations of craniofacial surgeons over 50 years.

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DISCLOSURE

Dr. Figueroa receives royalties from KLS Martin (Jacksonville, Fla.) and patent royalties from Stryker (Kalamazoo, Mich.). All

the other authors have no financial interest to declare in relation to the content of this article.

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