Treacher Collins Syndrome

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KEYWORDS

• Treacher Collins syndrome • Franceschetti-Klein syndrome • Malar hypoplasia
• Mandibular hypoplasia • Mandibular distraction • Congenital airway • Facial deformity • Microtia

KEY POINTS

- Treacher Collins syndrome presents a challenge to the craniofacial plastic surgeon with both significant functional and aesthetic considerations.
- Recent data have elucidated the multilevel anatomic complexity of the airway in Treacher Collins syndrome. Mandibular distraction osteogenesis is an effective option in select patients; however, tracheostomy at times cannot be averted.
- Facial manifestations of the syndrome can produce significant psychosocial impact. Surgical treatment to obviate stigma are continually being developed and refined.
- Patients with Treacher Collins syndrome should be referred to specialized centers with the comprehensive care of a multidisciplinary craniofacial team.
- As a rare disorder, there remains a paucity of high-level evidence as to the treatment protocol of patients with Treacher Collins syndrome.

BACKGROUND

Treacher Collins syndrome (TCS) is a congenital craniofacial disorder characterized by malar and mandibulomaxillary hypoplasia and periorbital anomalies.[1] Although its eponymous name is credited to Edward Treacher Collins, a British ophthalmologist who described the condition in 1900, its original description was by Thomson in 1846 followed by Berry in 1889. Later in 1949, Franceschetti and Klein reviewed the disorder and proposed the term "mandibulofacial dysostosis" (Franceschetti-Klein syndrome).[2–5] To classify the disorder based on embryogenesis rather than the anatomically descriptive (facial cleft) classification of Tessier, Van der Meulen referred to the disorder as "zygotemporoauromandibular dysplasia," whereby associated malformations such as microtia, not explained by an underlying cleft, could be accounted for.[6,7]

As is the case with rare disorders, there remains a paucity of high-level evidence regarding the treatment strategies targeting TCS dysmorphology.[8] With that in mind, the treatment of patients affected with TCS follows the principles that guide craniofacial surgery with other such diagnoses—bony manipulation as a foundation followed by soft tissue reconstruction. Priority is given to functional issues followed by aesthetic concerns as patients progress to facial maturity. Owing to the complexity and wide array of anomalies, the management of children born with TCS benefits from a multidisciplinary team approach. In addition to the craniofacial plastic surgeon, the expertise of specialists in ophthalmology, ear, nose, and throat specialist, speech pathology, audiology, orthodontics, genetics, respirology, pediatrics, and intensive care may be necessary. Patient and family counseling is of key importance to arrive at a satisfactory quality of life, because these patients

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will likely require multiple interventions throughout childhood and often into adulthood.[9]

This review is not meant to be an exhaustive summary of the craniofacial surgical techniques that have remained largely unchanged, but instead to summarize general treatment concepts and to highlight areas of significant evolution. Perhaps the single most impressive advance has been in our understanding of the complexities of the airway in this population, opening the doors to a new era of surgical techniques to treat this difficult problem.

GENETICS AND PATHOGENESIS

TCS is an autosomal-dominant disorder with variable penetrance.[10] With no gender predilection, the incidence is estimated at 1 in 50,000 live births.[11,12] Mutations in the TCOF1, POLR1D, and POLR1C genes are complicit in the development of TCS, with the majority showing mutations in the TCOF1 locus on chromosome 5q31.3-q33.3 encoding for the *Treacle* protein, resulting in deficient ribosome biogenesis and subsequent neural crest cell insufficiency. A subset of patients with the disorder display no mutations.[10] Moreover, some studies report an autosomal-recessive pattern of inheritance (POLR1C).[13] Sixty percent of cases show spontaneous or de novo mutations and 40% have family-specific mutations. No phenotype/genotype correlation has been shown.[10]

Patients born with the disorder show broad variability in phenotypic presentation. Whereas some patients can display mild periorbital deformity that can be clinically subtle, others demonstrate a more complete phenotype with severe periorbital anomalies (downward slanting palpebral fissures, canthal dystopia, and colobomas), maxillomandibular hypoplasia, and hairline displacement with variable forms of microtia (**Fig. 1**).[10] Notwithstanding the severity, the deformity is bilateral and generally symmetric. The main presenting features reflect that of the underlying malformation in structures developed from the first and second branchial arches.[1] Other malformations include microtia with associated conductive hearing loss and possible speech delay, mandibular hypoplasia, and retrognathia with possible airway sequelae and cleft palate (in 40% of cases).[14,15] Intellectual disability and other extrafacial anomalies (eg, cardiac malformations) have been reported in the context of the underlying genetic mutation.[10,16]

Genetic analysis remains the definitive method of diagnosis for TCS, either prenatally or postnatally.[17] The usefulness of prenatal ultrasound examination in the diagnosis of TCS has also been described. Despite having the ability to detect some of the characteristic facial features of TCS, ultrasound examination alone cannot differentiate between similar syndromes of facial dysostoses.[18–22] In addition, given that a subset of patients may have no genetic mutations, together with phenotypic variability and lack of phenotype–genotype correlation, the results of prenatal genetic testing must be interpreted cautiously.

AIRWAY AND MANDIBLE

Airway obstruction remains the main priority of management when present in this subset of patients. Pierre Robin sequence can be an underlying process in TCS airway compromise, resulting in obstructive sleep apnea or possibly life-threatening respiratory insufficiency.[8,23,24] In their cohort, Plomp and colleagues[25] found that 54%

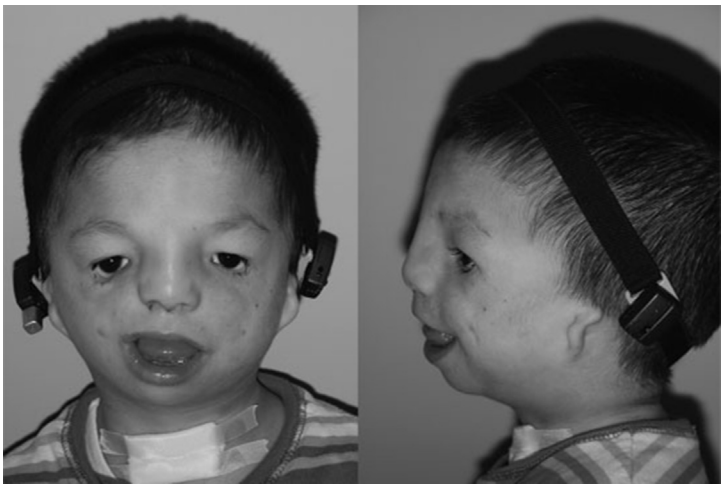

Fig. 1. Severe phenotype of Treacher Collins syndrome. (*Left*) periorbital malformations including downward slanting palpebral fissures and ectropion with scleral show. (*Right*) Microtia, low-lying ear remnants, and inferiorly displaced hairline. A band bone-anchored hearing aid is in place. (*From* Chang CC, Steinbacher DM. Treacher Collins syndrome. Semin Plast Surg 2012;26(2):84; with permission.)

of patients suffered from some form of obstructive sleep apnea, most being moderate, whereas Akre and colleagues[26] reported up to 95% of patients to be affected. Up to 78% of patients may display some form of mandibular involvement.[27,28] Any or all components of the mandible can be affected, including effacement of the mandibular angle, resulting in decreased posterior vertical height, a deep antegonial notch, and condylar aplasia with an aberrant temporomandibular joint.[29,30] Varying degrees of mandibular hypoplasia can be present.[31] When compared with hemifacial microsomia patients, the TCS mandibles as a whole were shown to be diminished volumetrically, exhibiting a volume comparable with Pruzansky type IIb and type III hemifacial microsomia mandibles.[32]

In severe cases, consultation with craniofacial surgeons will occur shortly after birth from the neonatal intensive care units. Focused evaluation typically begins with assessing positional oxygen saturation. Because the tongue proves to be relatively large in correlation to the oral cavity in the presence of micrognathia/retrognathia, desaturations are common in the supine position owing to aberrant oronasopharyngeal anatomy, glossoptosis, and airway obstruction.[33] Prone or decubitus positioning, as first-line management with or without a nasopharyngeal airway, can prove useful. If this is the case, outpatient management may be appropriate, because further growth of the mandible and airway will likely diminish the acute concern. If exogenous oxygen administration and/or positive airway pressure maneuvers are required, or if intubation is needed, further workup should be undertaken in the inpatient setting. Polysomnography, in addition to direct visualization methods such as laryngoscopy or bronchoscopy, are commonly used. These techniques help to delineate the cause of the apnea in question (central vs obstructive) and, more important, the level(s) of obstruction. In TCS, multiple anatomic airway anomalies are complicit in the obstructive pattern seen in certain patients.[23,34] Feeding difficulty should also be taken into account during patient assessment. Parenteral or enteral tube feeding methods may be required.

Surgical treatment, in the craniofacial context, is indicated if a compromised airway has been found to be due to a tongue-based obstruction or a diminished airway owing to retrognathia and mandibular hypoplasia, where the patient cannot be adequately managed by positioning or conservative measures alone.[35] Surgical procedures described include mandibular distraction osteogenesis, tongue–lip adhesion, and tracheostomy.[36–38] Genioplasty distraction osteogenesis with hyoid advancement has also been reported in patients who previously failed mandibular distraction.[39] The general goals of such surgical measures include decannulation or avoidance of tracheostomy and improvement of obstructive sleep apnea. Although correction of malocclusion and aesthetic differences (retrognathia) are sought, it is highly unlikely that such measures performed early in life for airway obstruction will persist into facial maturity and will likely have to be readdressed at a later stage.

Surgical planning includes preoperative imaging and direct airway assessment (flexible or rigid bronchoscopy) to rule out other airway anomalies that may be contributing to obstruction (including but not exclusive to laryngotracheomalacia, subglottic stenosis, vocal cord paralysis, septal deviation, choanal atresia, and hypertrophic adenoids).[33] Three-dimensional computed tomography imaging assists with the visualization of the anatomy and surgical planning (vectors of movement, osteotomy locations, etc), as well as an assessment of condylar or temporomandibular joint integrity.[30] Cephalometric radiographs can be useful in the context of assessing changes in craniofacial dimensions during and after treatment.

The TCS mandible should be addressed differently than patients with nonsyndromic Pierre Robin sequence, given the underlying morphology of the mandible.[40] The hypoplastic mandible in TCS can be deficient in 2 axes making the mandible uniplanar (**Fig. 2**).[41,42] In such cases, multivector distraction or curvilinear devices can be considered to address mandibular height and length in a single setting. Uniplanar devices, however, have also been demonstrated to have some usefulness in TCS cases in improving the 3-dimensional deficiency.[41] Regardless of technique, the timing of mandibular surgery remains debated. In cases where airway compromise is a factor, early distraction is an option to obviate the need for tracheostomy in select patients with adequate underlying anatomy. If airway is not a factor, then consideration can be given to delaying distraction or other facial osteotomies to maximize any native growth potential and decrease the need for repeat interventions owing to inevitable quantities of relapse, which can be significant or complete.

Recent studies have improved our understanding of the underlying complex airway anatomy in TCS patients that may predict the varying severity of the multifactorial airway obstruction. Ma and colleagues[23] have published 2 cross-sectional studies using 3-dimensional analyses to further clarify cephalometric changes in regard to cranial

	I	II	III	IV
SNB angle	Greater than 67°	62-67°	56-61°	Less than 55°
Co-Go-Me angle	Less than 135°	135-145°	146-155°	Greater than 155°
Condylar morphology	Normal	Morphologically normal, but hypoplastic/small	Condylar remnant that may not translate with glenoid fossa	Absent

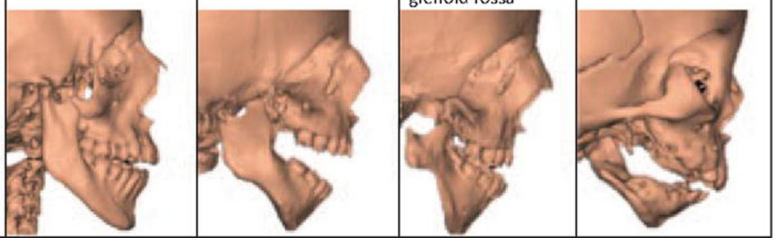

Fig. 2. Proposed classification of mandibular hypoplasia based on 3 categories: condylar morphology, retrognathia/sella–nasion–B point angle (SNB angle) and mandibular plane angle/Co-Go-Me angle. (*From* Ligh CA, Swanson J, Yu JW, et al, et al. A morphological classification scheme for the mandibular hypoplasia in Treacher Collins syndrome. J Craniofac Surg 2017;28(3):684; with permission.)

base, midface, and mandibular anomalous dimensions correlated with a smaller airway diameter.[34] Total upper airway volume was decreased by 30% with variability along its course; the most affected region being the retroglossal area. It was demonstrated that the length of the maxillary and mandibular bones, and anterior/posterior cranial base, were positively correlated with total airway volume. Alternatively, the mandibular projection (A-N-B angle) and the angle between the Frankfurt horizontal plane and mandible ramus plane (contributing to retrognathia) were negatively correlated. These results help to elucidate why mandibular distraction can (temporarily) improve airway patency. In a follow-up study by the authors focused on the nasal airway in this subset of patients, the nasal airway volume was found to be decreased by 40%. The most severely affected part is the anterior–inferior portion of the nasal cavity, demonstrating that transverse midface (ie, maxillary) hypoplasia, as well as its relative position or rotation, is a major factor.[23,34] Esenlik and colleagues[43] support this finding, reporting that retrognathia, decreased posterior facial height and an increase in the maxillary–mandibular plane angle were found to be correlated with the clinical severity of airway obstruction in the TCS population.

As mentioned elsewhere in this article, traditional techniques have focused on the surgical manipulation of the mandible alone. However, more recent airway data have delineated the contributory role of posterior facial height and the midfacial rotational deformity to the severity of airway obstruction.[29,44] To that end, recently a more innovative surgical approach has been described that addresses malposition of both the midface and mandible. Hopper and colleagues[45] examined the effectiveness of counterclockwise craniofacial distraction osteogenesis (coined C3DO) to reestablish airway patency and successfully decannulate tracheostomy-dependent patients, some of whom failed previous mandibular distraction osteogenesis. In their cohort, 5 patients with tracheostomies underwent Lefort II, mandibular osteotomies and maxilla–mandibular fixation with subsequent rotation of the subcranial facial skeleton as a unit using external midface and mandibular distractors (**Fig. 3**). The authors demonstrated successful decannulation in 4 of 5 patients with a complex airway. Although in its infancy, this technique represents a significant step forward in our improved understanding and surgical management of the unique complexities of the TCS airway.

DENTITION AND PALATE

Cleft palate occurs with an estimated incidence of one-third of TCS patients.[14] There are no published data to suggest that timing of cleft repair should be any different than non-TCS patients. However, it has been reported that these patients can suffer from a higher incidence of fistula formation after repair, perhaps related to suboptimal vascular perfusion of the mucosa.[46,47] Special emphasis has been placed on speech and language rehabilitation, because the surgical results may be suboptimal owing to the underlying hypoplasia and tissue quality.[46] Anatomic differences can pose some difficulty at the time of repair, including decreased oral aperture and a high arched palate.[17]

Malocclusion is another common finding in TCS. An incidence of up to 94% of patients

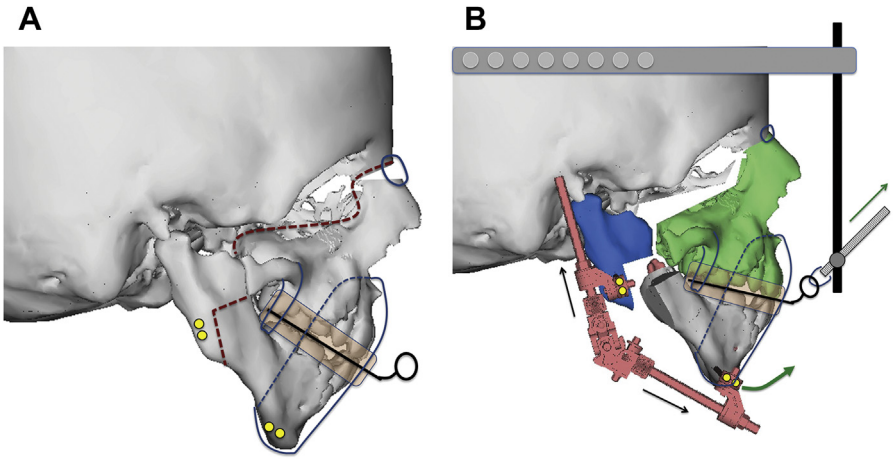

Fig. 3. Counterclockwise craniofacial distraction osteogenesis. (*A*) The Treacher Collins syndrome dysmorphology includes a clockwise rotation of the occlusal plane with associated airway deficit. (*B*) The subcranial skeleton is separated from the skull base through a Lefort II and bilateral mandibular osteotomies. A wire hinge is placed at the nasofrontal osteotomy and the patient is placed in maxillamandibular fixation. A midface distractor is attached to the maxillamandibular fixation splint and an external mandible distractor is placed with transfacial pins. The upward traction of the midface device creates a rotational force on the face and the mandible devices keep the mandibular condyle in position. Arrows: direction of pull. (*From* Hopper R, Kapadia H, Susarla S, et al. Counterclockwise craniofacial distraction osteogenesis (C3DO) for tracheostomy-dependent children with Treacher Collins syndrome. Plast Reconstr Surg 2018;142(2):449; with permission.)

demonstrating some form of malocclusion has been reported.[8] Typically, an anterior open bite with malpositioned teeth, often associated with a steep occlusal plane, is present.[17]

Some authors advocate the monitoring of dentition and oral hygiene as early as infancy, with subsequent orthodontic treatment once eruption of permanent teeth is complete.[48] Orthognathic intervention can take place during late adolescence. In the case of oral hygiene, one study concluded the presence of mild to severe salivary gland pathology in their cohort of 21 patients with TCS, resulting in oral dryness and higher prevalence of caries.[48]

PERIORBITAL FEATURES

Hypoplastic periorbital tissues are a hallmark of TCS (**Fig. 4**). The common finding of downward slanted palpebral (antimongoloid) fissures is related to lateral orbital wall hypoplasia/aplasia and the resultant canthal malposition.[17] Zygomaticomalar hypoplasia with a decrease in midfacial width and loss of normal protrusion of the cheeks is also common. Other periocular findings include colobomata of the lower eyelids and iris, ectropion, absence of eyelashes in the medial aspect of the lid, lacrimal system dysfunction or frank aplasia with resultant epiphora, strabismus, amblyopia, congenital cataracts, refractive errors, and/or vision loss.[17,49] The orbit is asymmetrically malformed, owing to the zygomatic hypoplasia.[50]

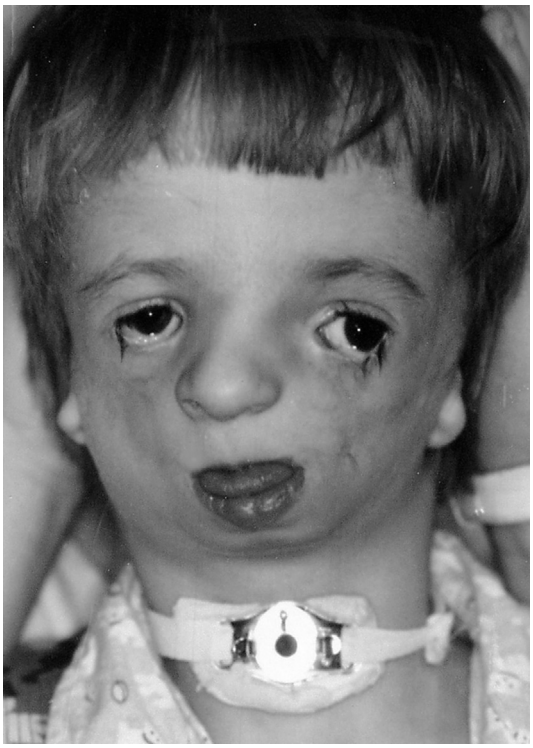

Fig. 4. A patient displaying a severe characteristic phenotype of Treacher Collins syndrome. Features include malar and mandibulomaxillary hypoplasia, periorbital soft tissue deficit with downward slanting palpebral fissures, lower lid colobomas, and ectropion. A tracheostomy is in place. (*From* Kobus K, Wojcicki P. Surgical treatment of Treacher Collins syndrome. Ann Plast Surg 2006;56(5):550; with permission.)

Surgical intervention is prioritized for procedures that minimize the risk of corneal desiccation and scarring (such as tarsorraphy), followed by those to address aesthetic deformities.[30] Techniques to correct lower lid abnormalities include Z-plasties, musculocutaneous advancement or transposition flaps (with or without prior tissue expansion) and canthopexy, among others.[28,51] Unfortunately, most described techniques are associated with visible scarring and contour deformities that are generally less than optimal.[1,27]

Zygomaticomalar hypoplasia is classically addressed with bone grafting, usually done in late childhood, with some authors advocating the procedures after the age of 7.[52] Fan and colleagues[52] have found a correlation between age of patient at time of grafting and degree of resorption, whereby as age increases, the likelihood of bony resorption decreases. Whereas costochondral grafts were used previously, newer data show a decreased rate of resorption when split or full-thickness calvarial bone grafts are used. McCarthy and colleague[53] has reported on the distraction of a bone graft used to augment the zygoma, obviating the need for repeat grafting, as is often required with this type of reconstruction given the degree of resorption and lack of growth potential. Another alternative is alloplastic reconstruction. Multiple reports have shown its usefulness, but it is not without risks commonly attributed to foreign material implantation, such as infection, malpositioning, migration, and extrusion.[54,55] Other techniques to correct midface hypoplasia that have been commonly described include Lefort I or II advancements to address the retropositioned maxilla.

Owing to the significant rates of resorption with nonvascularized bone grafting in the malar region, some authors have described the use of vascularized grafts, such as the temporal artery osteoperiosteal flap.[56] Despite its vascularized bony structure, the latter has been demonstrated to undergo significant resorption as well, limiting its popularity.[52]

In more recent years, fat grafting has increased in popularity owing to the minimal donor site morbidity and low-risk profile.[57] Harvest sites are similar to those in non-TCS patients; however, difficulty may arise in attempting to collect adequate amounts of adipose tissue, because these patients are commonly thin, with a slim body habitus.[8,58] Although requiring several sessions, fat grafting has proven to provide excellent malar volume augmentation, with early fat grafting advocated.[57]

Saadeh and colleagues[59] have reported on the use of free tissue transfer for the reconstruction of midface dysmorphology in patients with TCS, commonly from tissue harvested off the scapular system. Although effective in transporting significant volume to the face in a single setting, these patients required routine flap revisions to correct issues, such as sagging or volume asymmetry.

EAR MALFORMATION AND HEARING

Ear involvement is another common finding in TCS, with an incidence of anomalies reported up to 87%. Ears can show varying degrees of microtia, or in some cases, anotia. The position of the ears as well as the hairline can be low lying (in up to 48% of patients) (**Fig. 5**).[10] The external auricular deformity is commonly associated with a stenotic or atretic external auditory meatus and a malformed or absent middle ear.[17]

Up to 96% of patients are reported to have some degree of hearing loss.[10] A correlation between the severity of external auditory canal malformation and hearing impairment has been shown.[1] As a corollary, speech impairment may be present owing either to uncorrected hearing loss or other factors such maladaptive oral development.[60] In any case, an assessment by an ear, nose, and throat specialist, audiologist, and speech and language pathologist is essential.[46]

With regard to ear reconstruction, autologous methods have been advocated by most investigators, with the most commonly used techniques being those described by Nagata or Brent.[61,62]

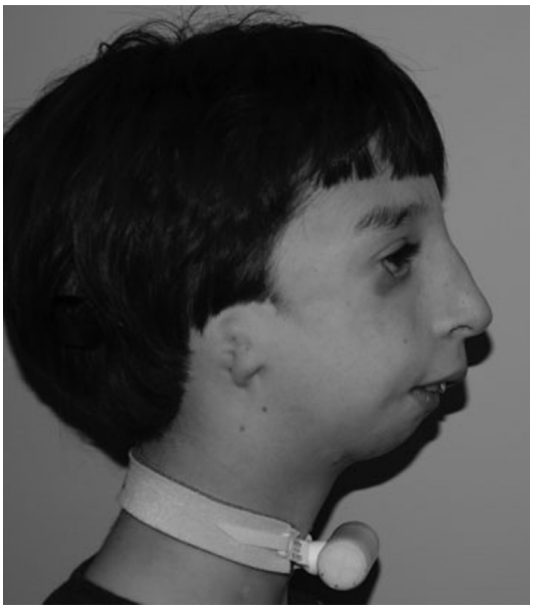

Fig. 5. Microtia in a patient with Treacher Collins syndrome. Low-lying ears and inferiorly displaced hairline are characteristic. (*From* Chang CC, Steinbacher DM. Treacher Collins syndrome. Semin Plast Surg 2012;26(2):85; with permission.)

Although autologous reconstruction remains as the most common technique, the use of porous polyethylene implants have also been described.[63] There is no evidence that the timing of surgery or the technique used should be any different with TCS patients as compared with other cohorts with microtia; however, the reconstruction of surrounding tissue, and the timing thereof, should be taken into account. Owing to the low-lying hairline characteristic of this subset of patients, laser hair removal has been advocated to ameliorate this concern.[10] The status of the superficial temporal artery affects decisions made for free tissue transfer.[64] Previous mandibular interventions should be noted, because this might affect the periauricular skin that is eventually included in microtia repair.[59,65] In addition, multidisciplinary planning is required to incorporate the ideal timing and location of bone-anchored hearing aid insertion if indicated as these 2 procedures may occupy similar anatomic real estate, causing some to place the fixture at a greater distance than usual from the meatus.[66] Another issue that can be faced is the insufficiency of calvarial bone thickness present in TCS patients that is not frequent in their nonsyndromic counterparts.[66]

Hearing impairment is typically addressed with removable bone-anchored hearing aid bands before definitive ear reconstruction.[30,66] This serves to prevent delay in language development, pending physical maturity to allow for definitive, commonly staged, ear reconstruction before conclusive osseointegrated bone-anchored hearing aid placement.[30]

SUMMARY

TCS is a complex multifaceted disorder that affects form and function. Patients suffering from the disorder should be referred to specialized centers that use a multidisciplinary team approach. Standard craniofacial techniques are the mainstay of current treatment protocols, although the type, timing, and role of mandibular surgery (distraction) continues to evolve. In addition, a more recent appreciation of the panfacial airway anomalies that contribute to the airway obstruction and aesthetic deformity will likely produce more stable and profound surgical correction of these anatomic issues. To that end, further research is still required to establish a more unified approach to this population.

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