Treacher Collins Syndrome: A Systematic Review of Evidence-Based Treatment and Recommendations

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Background: No reviews or guidelines are available on evidence-based treatment for the multidisciplinary approach in Treacher Collins syndrome. The authors' aim is to provide an evidence-based review of multidisciplinary treatment of Treacher Collins syndrome based on levels of evidence and supported with graded recommendations.
Methods: A systematic search was performed by means of the PubMed, Web-of-Science, Embase, and Cochrane Central databases (1985 to January of 2014). Included were clinical studies (with five or more Treacher Collins syndrome patients) related to therapy, diagnosis, or risk of concomitant diseases. Level of evidence of the selected articles was rated according to the American Society of Plastic Surgeons evidence-based clinical practice guidelines. After two panelists had reviewed each abstract separately, a consensus method was used to solve any disagreements concerning article inclusion.
Results: Of the 2433 identified articles, 63 studies (Level of Evidence II through V) were included. Conclusions and recommendations were extracted consecutively for the following items: upper airway; ear, hearing, and speech; the eye, eyelashes, and lacrimal system; growth, feeding, and swallowing; the nose; psychosocial factors; and craniofacial reconstruction.
Conclusions: In this systematic review, current evidence for the multidisciplinary treatment of Treacher Collins syndrome is provided, recommendations for treatment are made, and a proposed algorithm for treatment is presented. Although some topics are well supported, others, especially ocular, nasal, speech, feeding, and swallowing problems, lack sufficient evidence. In addition, craniofacial surgical reconstruction lacks a sufficient level of evidence to provide a sound basis for a full treatment protocol. Despite the rarity of the syndrome, more research is needed to compare outcomes of several surgical treatments, especially in orbitozygomatic/maxillary regions. (*Plast. Reconstr. Surg.* 137: 191, 2016.)

Treacher Collins syndrome is a rare congenital craniofacial condition.[1] Treacher Collins syndrome is an autosomal dominant disorder of craniofacial development with an estimated incidence of one in 50,000 live births.[2–4] Mutations in *TCOF1*, and in a smaller subset of Treacher Collins syndrome patients in *POLR1D* and *POLR1C*, are held responsible for the resulting phenotype; nevertheless, in some Treacher Collins syndrome patients, no mutations within these three genes are detected.[4–6] The subsequent craniofacial morphogenesis has a wide range of interfamilial and intrafamilial phenotypic variability.[7,8] Craniofacial deformities consist mostly of defects in the periorbital region and hypoplasia of the mandible and zygoma, microtia, and middle-ear deformities.

The rarity of the syndrome and the variety of the phenotypic expression make the multidisciplinary

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Received for publication January 20, 2015; accepted August 25, 2015.

DOI: 10.1097/PRS.0000000000001896

Disclosure: *The authors have no conflicts of interest to report.*

Supplemental digital content is available for this article. Direct URL citations appear in the text; simply type the URL address into any Web browser to access this content. Clickable links to the material are provided in the HTML text of this article on the *Journal*'s Web site (www.PRSJournal.com).

treatment challenging. Treatment currently is based on low levels of evidence consisting mainly of expert opinions (publishing their experience), case series, or retrospective cohort studies.[9–12] Although some authors present narrative reviews (i.e., overviews), generally these are not systematic and are opinion based, thereby suffering from the same limitations as expert opinion.[13–19] Because there is no clinical guideline or systematic review available, this study summarizes the current best-quality evidence and presents graded levels of recommendations with the aim of assisting physicians in their clinical decision-making and to explore the need for a multidisciplinary treatment approach in patients with Treacher Collins syndrome.

PATIENTS AND METHODS

A systematic search was performed in the PubMed, Web of Science, Embase, and Cochrane Central databases (1985 to January of 2014). The search terms "Treacher Collins," "mandibulofacial dysostosis," and "Treacher Collins Francescetti" and all possible combinations, truncations, and abbreviations were used. Databases were systematically searched consecutively and duplicates were omitted (Fig. 1). For PubMed, the following terms were used: (Treacher col*[tw] OR Franceschetti's syndrom*[tw] OR Franceschetti syndrom*[tw] OR Mandibulofacial Dysostos*[tw]). For Embase, the following terms were used: ((Treacher* NEXT/1 col*) OR (Franceschett* NEXT/1 syndrome*) OR (dysostos* NEAR/3 mandibul*)):de,ab,ti. For scopus, the following terms were used: (("Treacher col*" OR "Franceschetti syndrom*") OR (dysostos* NEAR/3 mandibul*)).

Level of evidence of the selected articles was rated according to the American Society of Plastic Surgeons evidence-based clinical practice

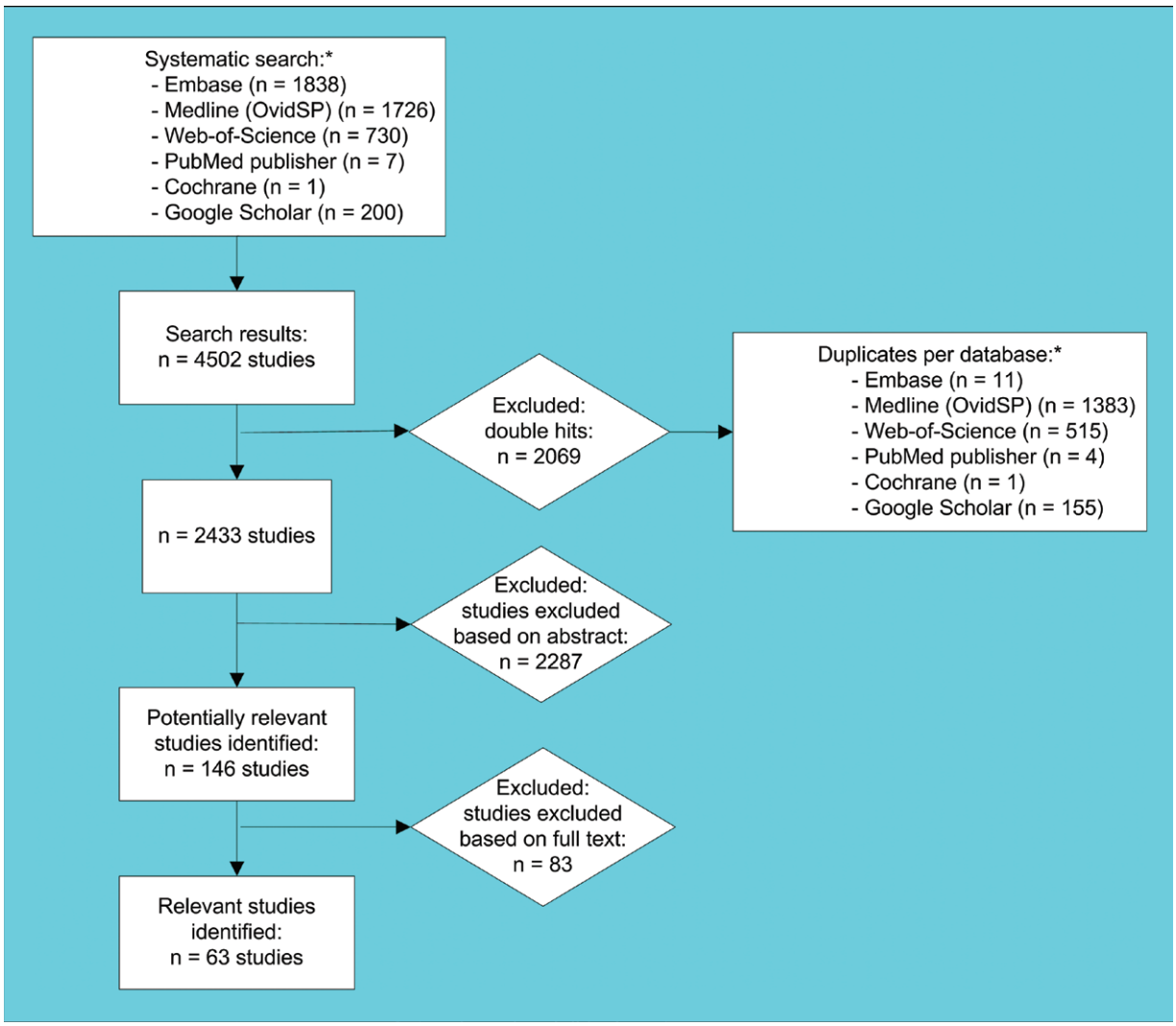

Fig. 1. Flowchart of the systematic literature search. * Databases were searched consecutively.

guidelines (Tables 1 through 4).[20,21] Two panelists (R.G.P. and M.J.S.L.) reviewed each abstract separately. Lists of abstracts found per topic of interest (the overview studies and the seven topics as described below) were reviewed critically between these two authors. Afterward, a consensus method between the panelists was used to solve disagreements concerning the inclusion.

Included were clinical studies related to therapy, diagnosis, or risk of concomitant diseases, with five or more Treacher Collins syndrome patients. Overview studies and seven topics were investigated: upper airway; the ear, hearing, and speech; the eye, eyelashes, and lacrimal system; growth, feeding, and swallowing; the nose; psychosocial factors; and craniofacial reconstruction. Tables were drawn up with all the studies included per topic of interest and a level of evidence was assigned. All authors of any specialty agreed on the assigned level of evidence. Excluded were case reports, studies with fewer than five Treacher Collins syndrome patients, book chapters, proceedings, studies not related to clinical practice, no abstract available, or inaccessibility of full text and/or non-English language texts.

Conclusions and recommendations were developed through a consensus process (all authors) and graded on the same levels of evidence by taking appropriate grades (A through D), according to the American Society of Plastic Surgeons. The consensus process consisted of a critical review for all topics of interest by all authors, and conclusions and recommendations were revised until all authors agreed.

RESULTS

The literature search (after deduplication) yielded 2433 articles (Fig. 1). Finally, 63 studies

Table 1. American Society of Plastic Surgeons Evidence Rating Scale for Therapeutic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multicentered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort or comparative study; or systematic review of these studies
III	Retrospective cohort or comparative study; case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

Table 2. American Society of Plastic Surgeons Evidence Rating Scale for Diagnostic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multicentered or single-centered, cohort study validating a diagnostic test (with "gold" standard as reference) in a series of consecutive patients; or a systematic review of these studies
II	Exploratory cohort study developing diagnostic criteria (with "gold" standard as reference) in a series of consecutive patient; or a systematic review of these studies
III	Diagnostic study in nonconsecutive patients (without consistently applied "gold" standard as reference); or a systematic review of these studies
IV	Case-control study; or any of the above diagnostic studies in the absence of a universally accepted "gold" standard
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research, or "first principles"

Table 3. American Society of Plastic Surgeons Evidence Rating Scale for Prognostic/Risk Studies

Level of Evidence	Qualifying Studies
I	High-quality, multicentered or single-centered, prospective cohort or comparative study with adequate power; or a systematic review of these studies
II	Lesser-quality prospective cohort or comparative study; retrospective cohort or comparative study; untreated controls from a randomized controlled trial; or a systematic review of these studies
III	Case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research, or "first principles"

Table 4. American Society of Plastic Surgeons Grades of Recommendation

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent	Generally, clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences.
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
D	Option	Level V: little or no systematic empirical evidence	Clinicians should consider all options in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

with different levels of evidence (range, II to V) were included. These results compiled "overview studies" addressing more than one topic and the seven topics of treatment (Table 5).[9–12,14–19,22–71] No randomized controlled trials were found.

DISCUSSION

Upper Airway

Obstructive sleep apnea is a known frequent finding in congenital craniofacial syndromes. Also, Treacher Collins syndrome patients suffer frequently from obstructive sleep apnea. Only three articles report on the prevalence of obstructive sleep apnea in Treacher Collins syndrome, each using different criteria (including a wide age range, and patients who already received treatment to improve breathing).[23,27,29] The reported prevalences were 25 percent,[30] 95 percent (11 percent tracheotomies),[27] and 46 percent [n = 35 tracheotomies (6 percent)],[23] respectively, despite several craniofacial operations related to the upper airway. Obstructive sleep apnea occurs in Treacher Collins syndrome children and adults[23] and there is no evidence for diminishing or changing prevalence and severity in the natural course of obstructive sleep apnea with aging. The level of severity ranged from mild to severe; severe obstructive sleep apnea syndrome was found in 25 to 41 percent.[23,27,29] Obstructions responsible for obstructive sleep apnea are found in the whole upper respiratory tract, that is, from nasopharyngeal to laryngeal level as observed through (sleep) endoscopy.[23,28]

Screening for obstructive sleep apnea in Treacher Collins syndrome based on the Epworth Sleepiness Scale in adults and the Brouillette score in children is unreliable, partially because a substantial number of the patients snore.[22,24] In general, questionnaires are unable to discriminate between snoring and obstructive sleep apnea or to determine the severity of obstructive sleep apnea.[72] In other studies, the results were unclear, because of including several syndromes and/or not reporting syndrome-specific results (bronchoscopy[26] and screening questionnaires[25]).

The incidence of cleft palate is estimated at 23 percent.[70] There is no specific evidence that timing of cleft repair should be different from that of other cleft palate syndromes or nonsyndromic cleft palate repair. A higher risk of palatal fistula is mentioned, although not much evidence is provided.[70] In a study researching several congenital craniofacial syndromes (including Treacher Collins syndrome), it is proposed that the presence of a cleft palate reduces the probability of a tracheotomy.[29] Another study reported delayed palatal repair in some cases resulting from complicated airway management in Treacher Collins syndrome.[9] Although it is assumed that closure of the cleft palate narrows the airway, the exact effect on obstructive sleep apnea of palate closure in Treacher Collins syndrome is unreported. However, it is advisable to precede palatal reconstruction by polysomnography with imitated closure to rule out potential severe respiratory distress. In case of respiratory problems, the palatal reconstruction should be delayed.[73,74]

In general, a tracheotomy necessary to secure the airway is reported in less than or equal to 41 percent.[23,29,36] Other options are continuous positive airway pressure or, in selected cases, a mandibular distraction osteogenesis. In mild obstructive sleep apnea, prone positioning can be considered, as in Pierre Robin sequence.[75] Other options for respiratory support are oxygen supplementation, Optiflow (Fisher & Paykel Healthcare, Melbourne, Victoria, Australia), continuous positive airway pressure, bilevel positive airway pressure, nasopharyngeal tube, or an endotracheal tube in acute

Table 5. Search Results for Evidence on Separate Topics in Treacher Collins Syndrome

Reference	Title of Article	Parameter(s) Addressed	LEBM
Overview studies			
Thompson et al., 2009[9]*	Treacher Collins syndrome: Protocol management from birth to maturity	n/a	IV
Miller and Schendel, 2006[10]*	Invited discussion: Surgical treatment of Treacher Collins syndrome	n/a	V
Kobus and Wojcicki, 2006[11]*	Surgical treatment of Treacher Collins syndrome	n/a	IV
Marszalek et al., 2002[15]	Clinical features, treatment and genetic background of Treacher Collins syndrome	n/a	IV
Posnick et al., 2004[14]*	Treacher Collins syndrome: Current evaluation, treatment and future directions	n/a	V
Freihofer, 1997[18]	Variations in the correction of Treacher Collins syndrome	n/a	V
Posnick, 1997[17]*	Treacher Collins syndrome: Perspectives in evaluation and treatment	n/a	V
Roncevic amd Roncevic, 1996[19]*	Mandibulofacial dysostosis: Surgical treatment	n/a	IV/V
Argenta and Iacobucci, 1989[16]*	Treacher Collins syndrome: Present concepts of the disorder and their surgical correction	n/a	V
Tulasne and Tessier, 1986[12]*	Results of the Tessier integral procedure for correction of Treacher Collins syndrome	n/a	V
Upper airway			
Geirdal et al., 2013[22]	Association between obstructive sleep apnea and health-related quality of life in individuals affected with Treacher Collins syndrome	Obstructive sleep apnea, quality of life	II
Plomp et al., 2012[23]	Obstructive sleep apnoea in Treacher Collins syndrome: Prevalence, severity and cause	Obstructive sleep apnea, prevalence, cause, and therapy	II
Plomp et al., 2012[24]	Screening for obstructive sleep apnea in Treacher Collins syndrome	Obstructive sleep apnea, screening methods	II
Luna-Paredes et al., 2012[25]	Screening for symptoms of obstructive sleep apnea in children with severe craniofacial anomalies: Assessment in a multidisciplinary unit	Obstructive sleep apnea, screening methods	IV
Anton-Pachecho et al., 2012[26]	The role of bronchoscopy in the management of patients with severe craniofacial syndromes	Obstructive sleep apnea, cause	IV
Akre et al., 2011[27]	Obstructive sleep apnea in Treacher Collins syndrome	Obstructive sleep apnea	II
Thompson et al., 2009[9]*	Treacher Collins syndrome: Protocol management from birth to maturity	Obstructive sleep apnea, prevalence	IV
Sorin et al., 2004[28]	Predicting decannulation outcomes after distraction osteogenesis for syndromic micrognathia	Obstructive sleep apnea, therapy	IV
Sculerati et al., 1998[29]	Airway management in children with major craniofacial anomalies	Obstructive sleep apnea, therapy	II
Sher et al., 1986[30]	Endoscopic observations of obstructive sleep apnea in children with anomalous upper airways: Predictive and therapeutic value	Obstructive sleep apnea, cause	IV
Hearing and speech			
Asten et al., 2013[31]*	Orofacial function and oral health associated with Treacher Collins syndrome	Speech problems, prevalence	II
Marsella et al., 2011[32]	Bone-anchored hearing aid (Baha) in patients with Treacher Collins syndrome: Tips and pitfalls	Hearing, therapy	III
Thomeer et al., 2010[33]	Isolated congenital stapes ankylosis: Surgical results of a consecutive series of 39 ears	Hearing, therapy	IV
McDermott et al., 2009[34]	Quality of life in children fitted with a bone-anchored hearing aid	Hearing, therapy	III
Vallino, 2006[35]*	The syndromes of Treacher Collins and Nager	Hearing and speech, therapy	V
Vallino-Napoli, 2002[36]*	A profile of the features and speech in patients with mandibulofacial dysostosis	Speech problems	II
Takegoshi et al., 2000[37]	Mandibulofacial dysostosis: CT evaluation of the temporal bones for surgical risk assessment in patients with bilateral aural atresia	Hearing, cause	II
Marres et al., 1995[38]	Ear surgery in Treacher Collins syndrome	Hearing, therapy	II
Taylor and Phelps, 1993[39]	Imaging of ear deformities in Treacher Collins syndrome	Hearing, cause	II
Pron et al., 1993[40]	Ear malformation and hearing loss in patients with Treacher Collins syndrome	Hearing, cause	II

(*Continued*)

Table 5. (*Continued*)

Reference	Title of Article	Parameter(s) Addressed	LEBM
Eye, eyelashes, and lacrimal system			
Thompson et al., 2009[9]*	Treacher Collins syndrome: Protocol management from birth to maturity	Visual disabilities, prevalence	II/V
Hertle et al., 1993[41]	Ophthalmic features and visual prognosis in the Treacher Collins syndrome	Visual disabilities, cause	II
Wang et al., 1990[42]	Ocular findings in Treacher Collins syndrome	Visual disabilities, lacrimal system, eyelashes, prevalence, cause	II
Bartley, 1990[43]	Lacrimal drainage anomalies in mandibulofacial dysostosis	Lacrimal system, cause	II
Growth, feeding, and swallowing			
Asten et al., 2013[31]*	Orofacial function and oral health associated with Treacher Collins syndrome	Speech, feeding difficulties prevalence	II
Osterhus et al., 2012[44]	Salivary gland pathology as a new finding in Treacher Collins syndrome	Salivary secretion, ultrasound features, oral dryness, prevalence, and cause	II
Vallino-Napoli, 2002[36]*	A profile of the features and speech in patients with mandibulofacial dysostosis	Speech problems, prevalence	II
Nose			
Plomp et al., 2015[45]	Nasal sequelae of Treacher Collins syndrome	Endonasal deformity, external nasal deformity, nasal complaints, prevalence	II
Farkas and Posnick, 1989[46]	Detailed morphometry of the nose in patients with Treacher Collins syndrome	External nasal deformity, prevalence	II
Psychosocial factors			
Plomp et al., 2013[47]	Long-term assessment of facial features and functions needing more attention in Treacher Collins syndrome	Satisfaction with facial features and functions, prevalence	II
Bemmels et al., 2013[48]	Psychological and social factors in undergoing reconstructive surgery among individuals with craniofacial conditions: An exploratory study	Psychological and social implications of craniofacial surgery, prevalence	IV/V
van den Elzen et al., 2012[49]	Assessing nonacceptance of the facial appearance in adult patients after complete treatment of their rare facial cleft	Acceptance of deformity, correlation with facial deformity, prevalence	II
van den Elzen et al., 2012[50]	Adults with congenital or acquired facial disfigurement: Impact of appearance on social functioning	Social functioning, predictors, cause	II
Van den Elzen et al., 2012[51]	Defense mechanisms in congenital and acquired facial disfigurement: A clinical-empirical study	Coping mechanisms, cause	II
Versnel et al., 2012[52]	Long-term psychological functioning of adults with severe congenital facial disfigurement	Long-term psychological functioning, predictors, prevalence, cause	II
Beaune et al., 2004[53]	Adolescents' perspectives on living and growing up with Treacher Collins syndrome: A qualitative study	Social functioning, prevalence	IV
Barden et al., 1988[54]	The physical attractiveness of facially deformed patients before and after craniofacial surgery	Physical attractiveness, social functioning, treatment	II
Barden et al., 1988[55]	Emotional and behavioral reactions to facially deformed patients before and after craniofacial surgery	Social functioning, surroundings, treatment	II
Arndt et al., 1987[56]	Psychosocial adjustment of 20 patients with Treacher Collins syndrome before and after reconstructive surgery	Social functioning, effect of surgery, treatment	II
Craniofacial reconstruction			
Upper face			
Nikkhah et al., 2013[57]	Planning surgical reconstruction in Treacher Collins syndrome using virtual simulation	Surgical reconstruction, CT scan, diagnosis	V
Nikkhah et al., 2013[58]	A classification system to guide orbitozygomatic reconstruction in Treacher Collins syndrome	Surgical reconstruction, diagnosis	V
Fan et al., 2012[59]	Optimizing the timing and technique of Treacher Collins orbital malar reconstruction	Surgical malar reconstruction, treatment	IV
Thompson et al., 2009[9]*	Treacher Collins syndrome: Protocol management from birth to maturity	Surgical reconstruction/treatment overall	V
Kobus and Wojcicki, 2006[11]*	Surgical treatment of Treacher Collins syndrome	Surgical reconstruction overall, treatment	V

(*Continued*)

Table 5. (*Continued*)

Reference	Title of Article	Parameter(s) Addressed	LEBM
Miller and Schendel, 2006[10]*	Invited discussion: Surgical treatment of Treacher Collins syndrome	Surgical reconstruction overall, treatment	V
Posnick et al., 2004[14]*	Treacher Collins syndrome: Current evaluation and treatment	Surgical reconstruction overall, treatment	V
Posnick and Ruiz, 2000[13]	Treacher Collins syndrome: Current evaluation, treatment, and future directions	Surgical reconstruction overall, treatment	V
Posnick, 1997[17]*	Treacher Collins syndrome: Perspectives in evaluation and treatment	Surgical reconstruction overall, treatment	V
Ronsevic and Ronsevic, 1996[19]*	Mandibulofacial dysostosis: Surgical treatment	Surgical reconstruction overall, treatment	IV/V
Posnick et al., 1993[60]	Surgical correction of the Treacher Collins malar deficiency: Quantitative CT scan analysis of long-term results	Surgical malar reconstruction, treatment	IV
Argenta and Iacobucci, 1989[16]*	Treacher Collins syndrome: Present concepts of the disorder and their surgical correction	Surgical reconstruction overall, treatment	V
Midface			
Kapadia et al., 2013[61]	Cephalometric assessment of craniofacial morphology in patients with Treacher Collins syndrome	Morphology, diagnosis	II
Saadeh et al., 2008[62]	Microsurgical correction of facial contour deformities in patients with craniofacial malformations: A 15-year experience	Microsurgical flap reconstruction, treatment	IV
Saadeh et al., 2006[63]	A soft-tissue approach to midfacial hypoplasia associated with Treacher Collins syndrome	Parascapular flap reconstruction, treatment	IV
Freihofer, 1997[18]	Variations in the correction of Treacher Collins syndrome	Surgical reconstruction overall, treatment	IV
Roddi et al., 1995[64]	Treacher Collins syndrome: Early surgical treatment of orbitomalar malformations	Orbitomalar reconstruction, treatment	IV
Tulasne and Tessier, 1986[12]*	Results of the Tessier integral procedure for correction of Treacher Collins syndrome	Maxillomandibular reconstruction, treatment	V
Lower face			
Terner et al., 2012[65]	An analysis of mandibular volume in Treacher Collins syndrome	Morphometry, diagnosis	II
Steinbacher et al., 2011[66]	Relation of the mandibular body and ramus in Treacher Collins syndrome	Morphometry, diagnosis	II
Miloro, 2010[67]	Mandibular distraction osteogenesis for pediatric airway management	Mandibular distraction, treatment	III
Shetye et al., 2009[68]	Documentation of the incidents associated with mandibular distraction: Introduction of a new stratification system	Mandibular distraction, treatment	II
Heller et al., 2006[69]	Genioplasty distraction osteogenesis and hyoid advancement for correction of upper airway obstruction in patients with Treacher Collins and Nager syndromes	Genioplasty and hyoid advancement, treatment	IV
Bresnick et al., 2003[70]	Increased fistula risk following palatoplasty in Treacher Collins syndrome	Palatoplasty, treatment	III
Stelnicki et al., 2002[71]	Long-term outcome study of bilateral mandibular distraction: A comparison of Treacher Collins and Nager syndromes to other types of micrognathia	Mandibular distraction, treatment	IV

LEBM, level of evidence-based medicine according to the American Society of Plastic Surgeons; CT, computed tomographic.
*This article is applicable and listed in two or more topics.

severe respiratory distress.[75] (**See Figure, Supplemental Digital Content 1**, algorithm for treatment of Treacher Collins syndrome, ***http://links.lww.com/PRS/B512.***) Although one study showed a correlation between obstructive sleep apnea severity and diminished health-related quality of life, it included few participants, and facial deformity was an important confounding factor.[22]

Ear, Hearing, and Speech

Although patients with Treacher Collins syndrome (and other craniofacial syndromes) can suffer from hearing loss, delay of appropriate treatment and thus hearing rehabilitation is still often encountered.[76,77] Approximately 93 to 96 percent of Treacher Collins syndrome patients suffer from a unilateral or bilateral conductive hearing loss. Seven percent suffer from a mixed hearing loss.[36,40] Hearing loss is moderate (41 to 55 dB hearing loss) to moderately severe (56 to 70 dB hearing loss),[36] the latter being reported in up to 65 percent.[9] Patients themselves often report hearing impairment (95 percent) and approximately 50 percent report communication difficulties.[31]

Computed tomographic findings reveal complex, often combined deformities to the

external auditory canal, the middle ear cavity, and the inner ear. The external auditory canal is shown to be normal (0 to 15 percent), stenotic (28 to 31 percent), and atretic (54 to 72 percent). Middle ear cavity deformities are usually symmetric and consist of hypoplastic, ankylosed ossicles (33 to 82 percent) or missing ossicles (22 to 67 percent), particularly the malleus and incus.[37–40] The inner ear is developed normally in most cases (78 to 100 percent),[37,39,40] the mastoid rarely shows pneumatization.[37–39] The facial nerve sometimes runs a deviant course, complicating middle ear surgery.[31,38,39] Unfortunately, the outcome of reconstructive ear surgery is often disappointing, and effective hearing improvement is achieved in only a minority.[33,38]

The bone-anchored hearing aid offers significant hearing improvement compared with conventional bone-conduction hearing aids (in total, 39 dB versus 29 dB); also, its insertion has a low complication rate.[32] In addition, one study showed improved quality of life related to behavior, concentration, learning, and development.[34] A banded hearing aid is an option for the first few years of life. In general, a bone-anchored hearing aid should not be placed before 3 years of age.[78]

Speech development is frequently impeded in patients with Treacher Collins syndrome, although reported evidence is scarce.[9,35,36] One study showed that speech errors often consist of overlapping causes, related (in approximately 60 percent) to malocclusion, palatopharyngeal incompetence (30 percent) and errors in the general articulatory/phonologic category, or hearing loss (50 percent).[36] Hypernasality (palatopharyngeal incompetence) and hyponasality (restricted nasal cavities and/or choanal atresia), but also mixed resonance patterns, are found.[36] Patients are dissatisfied with their speech/quality of phonation compared with controls.[47]

Autologous external ear reconstruction could start at 9 years, and prosthetic devices are an option. However, the results of both are found to be dissatisfying in one study.[47] Moreover, the autologous reconstruction is impeded by a low hair implant and the limited options of reconstruction caused by unavailability of the temporofacial flap if used earlier in pedicled bone grafts for the zygoma.

Eye, Eyelashes, and Lacrimal System

Although periorbital soft-tissue defects are well known, true ophthalmologic sequelae are seldom mentioned.[9,13,14] However, there is evidence for vision loss (37 percent), amblyopia (33 percent), significant refractive errors (58 percent), and anisometropia (17 percent).[41] Another study found bilateral absence of the inferior lacrimal puncta (36 percent), cilia (50 percent), scleral show (50 percent), refractive errors (86 percent), regular astigmatism (36 percent), and absent lateral canthal tendon (64 percent).[42] Absent inferior lacrimal puncta, normal superior lacrimal puncta, and intermittent or constant tearing were found in 71 percent.[43] One overview reported downslanting palpebral fissures in all and "visual disability" in approximately one-third.[9] Although Treacher Collins syndrome patients are dissatisfied with the aesthetic appearance of their eyelids, they are not dissatisfied with their vision compared with controls.[47] Musculocutaneous transposition flaps, Z-plasties, and lateral canthopexy[9–17,19] can be used to reconstruct the periorbital soft-tissue deformities; they are frequently applied but often lead to scarring, contour deformities, and low patient satisfaction of the residual deformity.[47] Colobomas need special attention at an early age from birth onward because they form a potential threat to vision through corneal drying. A defect larger than one-third of the eyelid margin is an indication for timely surgery.[79]

Growth, Feeding, and Swallowing

Feeding issues are common in patients with craniofacial syndromes. However, direct evidence of orofacial dysfunctioning in Treacher Collins syndrome is scarce. Treacher Collins syndrome patients are generally rather thin, suggestion a feeding problem..[23] One study found reduced jaw opening (63 percent), malocclusion (94 percent), narrow hypopharynx (84 percent), eating difficulties as reported by patients (68 percent), and dry oral mucosa (42 percent).[31] The latter may be partially explained by the salivary gland abnormality, found in 48 percent. Dysplasia of the parotid and the submandibular gland was found in 29 percent and total aplasia was found in 19 percent of Treacher Collins syndrome patients. Over 50 percent had no parotid gland secretion, and the orifice of the Stenson duct was often not detectable.[44]

Nose

Currently, there is limited evidence for endonasal and external nasal deformities and associated dysfunctional and aesthetic sequelae. The clinical picture suggests a pollybeak deformity and a dorsal hump deformity.[9–11,80] The main external nasal deformities were the dorsal hump (73 percent), external deviation (≤55 percent), bifid or bulbous tip (55 percent), and columellar septal

luxation (55 percent).[45] In 82 percent, a septal deviation was found, sometimes contributing to nasal obstruction.[45] A septorhinoplasty is advised from age 17 years onward.[13,14,81] One study showed an 11 percent prevalence of choanal atresia.[9] In 1989, Farkas and Posnick performed measurements (age range, 6 to 21 years); in most patients, the nose height and width were optimal, although a protruded proximal part of the nose and a relatively wide/deep nasal root were also found.[46] Another study reports patients who are relatively satisfied with the various aesthetic subunits of the nose compared with a control group. The most significant functional problem was snoring.[24]

Psychosocial Factors

Evidence for psychosocial problems is very limited.[56] Adults with congenital rare facial clefts appear to have relatively "normal" long-term psychological functioning. However, stigmatization and insecurity about possible negative reactions of others can elicit stress and avoidance behavior.[50,63] Important predictors for long-term psychological functioning are fear of negative appearance evaluation, self-esteem, and patients' satisfaction with facial appearance.[52] In addition, self-esteem is an important predictor to differentiate between "mature" (recognition of a threat and dealing with it) and "immature" (denial and externalization) psychological defense mechanisms.[51] Interestingly, objective severity of the deformity is not a predictor for patients' acceptance of the deformity or for long-term psychological functioning. However, compared with a nonaffected population, Treacher Collins syndrome patients remain less satisfied about several facial subunits (i.e., ears, facial profile, eyelids, and chin).[47] Congenital craniofacial patients less frequently have a partner or children and are prone to internalizing behavior problems.[52] Risk factors for not accepting the final surgical result are self-perceived visibility of the deformity, a troublesome puberty, an emotional coping style, and facial functional problems.[49] Importantly, these functional problems especially occur frequently in Treacher Collins syndrome.[47] In mixed craniofacial groups, surgery seems to positively affect patients' attractiveness,[55] satisfaction with facial appearance,[56] and reactions to their surroundings.[54]

Craniofacial Reconstruction

Craniofacial reconstruction is the most challenging part of treatment in Treacher Collins syndrome. Many experts have published their opinion/narrative review, including the Tessier integral procedure.[9–18]

Upper Face and Midface

Calvarial bone grafts are generally used for zygomatic reconstruction and orbital floor and lower rim repair, either as free grafts or as pedicled flaps.[60,64] A disadvantage is resorption of calvarial bone grafts for zygomatic reconstruction, which occurs in almost all patients.[59]

The hypoplastic maxilla is positioned posteriorly in relation to the cranial base.[61] Techniques for correcting midface hypoplasia are the Le Fort I procedure (age older than 16 years), Le Fort II procedure with cranial bone grafts (described at several ages[12]), augmentation with rib grafts,[19] or the malar osteotomy[18] with or without onlay autologous grafts[58] or lipofilling. Although limited, there is some evidence for a safe and reliable malar reconstruction using parascapular free flap transfer.[62,63] However, microvascular free flaps can be bulky, have a tendency to sag, and may require multiple revisions for thinning and resuspension as in, for example, progressive hemifacial atrophy. Lipofilling can be a treatment of choice in these syndromes.[82] Inorganic implants might be an option but may be, as with inorganic implants in general, more prone to infection and dislocation.[83]

Lower Face

The mandible in Treacher Collins syndrome is retrognathic: the ramus is short, the ramus body angle is more obtuse, the mandibular plane angle is more steep, and a deep antegonial notch is often present.[65,66] There is evidence for safe mandibular lengthening at age 1 to 4 years with distraction osteogenesis[71] to correct the pediatric compromised airway resulting from the congenitally retrognathic mandible.[67,68] A small study ($n = 5$) reported that genioplasty distraction osteogenesis combined with hyoid advancement might also be favorable in Treacher Collins syndrome, in case mandibular distraction fails to reduce the upper airway obstruction.[69] Patients cannot always be decannulated after mandibular distraction, probably because of multilevel obstructions.[28] Throughout the years, a thorough dental/orthodontic screening is necessary to monitor malocclusion and dental crowding. Orthodontic treatment may be indicated preoperatively and/or postoperatively regarding mandibular and/or maxillary surgery.[9,13,14]

Grading Systems

Some subjective grading systems have been described for grading Treacher Collins syndrome. Hayashi et al. described a scoring system with eight criteria (facial features and the *TCOF1* mutation).[84] The second is the O.M.E.N.S. (i.e., orbital distortion, mandibular hypoplasia, ear anomaly, nerve

involvement, and soft-tissue deficiency) classification, as initially proposed for craniofacial microsomia, indicating five major facial features.[85] A third, more recently proposed expert opinion–based orbitozygomatic classification system indicates four types of severity and their advised reconstruction.[58] Although all of these classification systems illustrate the variety and severity of the deformities, these classifications have never shown a predictive value with regard to functional problems and/or timing and type of treatment; therefore, they are rarely used in clinical practice.

Altogether, the main targets of the multidisciplinary treatment of Treacher Collins syndrome should be early recognition of obstructive sleep apnea through polysomnography and a thorough ear, nose, and throat examination to determine the level of upper airway obstruction (Table 6 and **Figure, Supplemental Digital Content 1,** algorithm for treatment of Treacher Collins syndrome, ***http://links.lww.com/PRS/B512***). The results of these examinations should determine the next steps in treatment. In mild obstructive sleep apnea, prone positioning can be considered. In moderate/severe obstructive sleep apnea, the options for respiratory support are oxygen supplementation, Opti-Flow, continuous positive airway pressure, bilevel positive airway pressure, and a nasopharyngeal tube. In acute severe respiratory distress, other options may reside in an endotracheal tube. (**See Figure, Supplemental Digital Content 1,** algorithm for treatment of Treacher Collins syndrome, ***http://links.lww.com/PRS/B512***.) After adequate respiratory support, an endoscopy of the upper airway indicates the level of upper airway obstruction. Hereafter, a tracheotomy and/or other upper airway surgery could be considered. A reevaluation of respiratory distress is advised every 3 to 6 months.

Table 6. Conclusions and Recommendations for Treatment of Treacher Collins Syndrome

Topic	Evidence Rating Scale (I–V)* or Grade of Recommendation (A–E)†
Upper airway	
Conclusions	
In TCS, OSA is frequently present at all ages and is often severe	II
OSA has a multilevel origin in TCS	II
Screening for OSA in TCS based on the Epworth Sleepiness Scale in adults and the Brouillette score in children is not reliable	II
Recommendations	
A (laboratory) polysomnogram is mandatory for all newly referred TCS patients, regardless of their age	B
In TCS, determination of the level of obstruction in patients with severe OSA is important; flexible laryngoscopy at the outpatient clinic by an ENT specialist can be the first approach	C
In pediatric TCS patients, sleep endoscopy may be useful to determine the level of obstruction	C
Surgical treatment of OSA should be adjusted to the right level of obstruction, although a tracheotomy is sometimes inevitable in severe OSA	C
Every 3–6 mo, respiratory distress should be reevaluated and treatment reconsidered	D
Ear, hearing, and speech	
Conclusions	
TCS patients mainly suffer from moderate to severe conductive bilateral hearing loss	II
BAHA implantation results in significant improvement of hearing	II
Because of the complex external auditory ear canal and middle ear deformities underlying the hearing loss, successful reconstructive ear surgery is difficult	IV
Speech problems are common in TCS, and patients are often dissatisfied with their speech/quality of phonation	II
An interaction between anatomical defects, malocclusion, and hearing loss results in impaired speech	IV
Recommendations	
Starting at 3 mo of age and older (as indicated), a thorough ENT screening, consisting of otoscopy and audiometry, seems advisable in TCS	B
A BAHA (from age 4 yr onward) seems inevitable for appropriate hearing rehabilitation and precedes external ear reconstruction later	B
A CT scan can help establish the severity of the middle ear deformities when considering reconstructive surgery and the thickness of the temporal bone before implanting a BAHA	C
Consultation with a speech and language therapist is mandatory, starting at age 2 yr	C

(*Continued*)

Table 6. (*Continued*)

Topic	Evidence Rating Scale (I–V)* or Grade of Recommendation (A–E)†
Eye, eyelashes, and lacrimal system	
Conclusion	
Refractive errors, scleral show, absent lateral canthal tendons, frequent tearing, and colobomas frequently occur	II
Recommendations	
An ophthalmologic screening at a young age (±1 yr) and regular follow-up are recommended	C
Indications for correction of eyelid deformities are imminent functional problems such as corneal erosion, dehydration, and closure problems; multiple corrections are often necessary; patients need to be informed about residual deformity	B
Growth, feeding, and swallowing	
Conclusion	
There is limited evidence for feeding and swallowing problems in TCS; a combination of orofacial anatomical deformities seems responsible for the reported eating difficulties	III
Recommendation	
A regular follow-up of growth (height/weight) is mandatory; in case of reported difficulties, monitoring of feeding, and consultation with a speech and language pathologist and dietician, are recommended	C
Nose	
Conclusions	
The main external nasal deformities are a dorsal hump, external deviation, and a bifid or bulbous tip	II
In most patients, a septal deviation can be found	IV
Snoring is frequently reported by patients	II
Recommendation	
In case of a significant septal deviation and concomitant complaints of nasal obstruction, a septal correction can be performed after the pubertal growth spurt	C
Psychosocial factors	
Conclusions	
There is evidence that patients with congenital craniofacial conditions have relatively normal long-term psychological functioning; however, isolated evidence for TCS patients is not provided	II
TCS patients are less satisfied with several parts of their face in the long term after surgery (i.e., ears, facial profile, and eyelids)	II
In a congenital craniofacial population, important predictors for long-term psychological functioning are self-esteem, satisfaction with facial appearance, and fear of negative appearance evaluation	II
Recommendations	
Creating realistic expectations concerning postoperative results is generally accepted but seems especially applicable to congenital craniofacial patients	B
At approximately age 4 yr, it is recommended that a psychologist be consulted to evaluate acceptance and self-esteem and affect predictors as mentioned of importance	C
Parents of TCS patients can be counseled on how to make children assertive and better cope with the reactions of others	D
Craniofacial reconstruction	
Conclusions	
There is insufficient evidence for a standard surgical treatment of the craniofacial malformations in TCS	n/a
Recommendations	
Indications for treatment of (severe) maxillary hypoplasia are malocclusion, airway obstruction at this level, and improvement of facial profile and lower eyelid support	D
Orbitozygomatic reconstruction can be performed by osteotomies, (vascularized) calvarial bone grafts, rib cartilage grafts, implants (particularly in adults), and/or lipofilling	D
Indications for mandibular surgery are severe airway obstructions at the tongue base level, malocclusion, and severe feeding problems; treatment can consist of a Le Fort I or mandibular distraction to overcome larger distances; a genioplasty is chosen for patients with mild deformities and no evident OSA	D
Timing of surgery is individualized and based on severity of functional problems	C

OSA, obstructive sleep apnea; TCS, Treacher Collins syndrome; ENT, ear, nose, and throat; BAHA, bone-anchored hearing aid; CT, computed tomographic; n/a, not applicable.
*Level of evidence-based medicine according to the American Society of Plastic Surgeons.
†Grades of recommendations according to the American Society of Plastic Surgeons.

Before closure of a cleft palate, a sleep study should be performed with imitated closure to rule out potential severe respiratory distress. Weight gain and feeding need close monitoring and require the help of a dietician and (prelingual) linguist. Specific attention should be paid to hearing and speech at an early stage so that treatment can be started as soon as possible.

In addition, an ophthalmologist should be consulted to identify and treat intraocular and ocular deformities. There exists considerable dissatisfaction with (residual) deformity after craniofacial surgery. Counseling of psychological sequelae and creating realistic expectations for the patient seem essential. There is insufficient evidence on surgical reconstruction for providing an evidence-based treatment protocol, but a proposed treatment algorithm was made. (**See Figure, Supplemental Digital Content 1, *http://links.lww.com/PRS/B512*.**)

Because of the rarity of the syndrome, it is recommended that medical care of these patients be centralized in a craniofacial center nationwide or statewide. This provides conjoined expertise of physicians and more possibilities for research to compare outcomes of different treatment modalities.

Limitations

This systematic review is limited by the low evidence level provided for treatment of Treacher Collins syndrome until now. Current (recommendation for) treatment is based on an interpretation of the evidence together with good clinical practice.

CONCLUSIONS

This systematic review provides current evidence for the multidisciplinary treatment of Treacher Collins syndrome, makes recommendations for treatment, and proposes an algorithm for treatment. Although some topics are well supported, others, especially ocular, nasal, speech, feeding, and swallowing problems, lack sufficient evidence. In addition, craniofacial surgical reconstruction lacks a sufficient level of evidence to provide a sound basis for a full treatment protocol. Despite the rarity of the syndrome, more research is needed to compare outcomes of several surgical treatments, especially in orbitozygomatic/maxillary regions.

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ACKNOWLEDGMENTS

This study was supported by the Nuts-Ohra Foundation (a Dutch health insurance organization) and the Stichting Hoofdzaak (a foundation for research on craniofacial malformations). These organizations had no involvement in the study design, in the collection and interpretation of data, in the writing of the manuscript, and/or the decision to submit the manuscript for publication. The authors thank Wichor Bramer, specialist in biomedical information, for the structured search strategies.

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