Clinical Implications of Treacher Collins Syndrome

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Clinical Implications of Treacher Collins Syndrome

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GENERAL INTRODUCTION

Chapter I

General introduction of the thesis

BACKGROUND

Treacher Collins syndrome (OMIM 154500) is a rare congenital craniofacial condition.[1] The incidence of Treacher Collins syndrome is nowadays estimated at 1 in 50,000.[2-3] Based on this, every year approximately 4-5 patients are born with this syndrome in the Netherlands.

Treacher Collins syndrome has several eponyms, for example it is also known as Franceschetti-Zwahlen-Klein syndrome or Berry syndrome. George Andreas Berry in 1889 first described an abortive form with colobomata of the lower eyelids. In 1900 Treacher Collins presented two similar cases and described their features (Figure 1).[4] Forty-four years later in 1944 Franceschetti and Zwahlen and later Franceschetti and Klein published a review with phenotypic features and designated it "mandibulofacial dysostosis".[5] In addition, later on Fazen described in 1967 10 affected persons in four

Figure 1. Illustration from the original report in 1900 of what is now called Treacher Collins syndrome.

generations.[1] Nowadays "Treacher Collins syndrome" (TCS) is the most used eponym for this congenital craniofacial syndrome.

Edward Treacher Collins

Edward Treacher Collins (1862-1932) was a British ophthalmologist (Figure 2). Collins went to university college London and started in 1879 at Middlesex Hospital where he received his medical degree in 1883. For 48 years Collins worked as a faculty member in

Figure 2. Edward Treacher Collins.

the Moorfields Eye Hospital. Collins contributed considerably to the ophthalmological community in that time.[6] One of his most important works is "The anatomy and pathology of the eye" published in 1900.[7]

Genetics

TCS is a mandibulofacial dysostosis syndrome with overlapping phenotypic facial clinical features syndromes with Miller syndrome (OMIM 263750) and Nager syndrome (OMIM 154400), distinguished by postaxial and preaxial deficiencies in the limbs respectively. Craniofacial microsomia (OMIM 164210) can resemble TCS phenotypic facial features, but these features are found mostly unilateral and in addition to craniofacial anomalies, there may be cardiac, vertrebral and central nervous system defects. Phenotypic facial features of TCS could be part of the Robin sequence (OMIM 261800). Until now three genes have been found responsible for the occurrence of the phenotypic features defining TCS. The inheritance of TCS is autosomal dominant. Mutations in *TCOF1* (78-93%) and in a smaller subset of TCS patients in *POLR1D* and *POLR1C* (8%) are found responsible for the resulting phenotype.[8-11] Sixty percent of the mutations are de novo in the *TCOF1*

gene.[12] Over 100 distinct mutations are identified.[3, 13] However, there still remain patients resembling the phenotype in whom no mutations within one of these three genes are detected, and thus the diagnosis TCS is only based on clinical features in these patients.

It is hypothesized that *TCOF1* (5q32-33.1) encodes *Treacle,* a protein which expression is crucial for craniofacial development via survival and migration of craniofacial neural crest cells resulting in first and second branchial arch cartilage, connective tissue, bone and nervous structures hypoplasia.[13-15] In addition, recently *TCOF1* is identified as a DNA damage response factor that suppresses inappropriate ribosomal DNA transcription and maintains genomic integrity after DNA damage.[16] The *POLR1D* gene (13q12.2) codes for three exons and *POLR1C* gene (6p21.1) codes for nine exons both contributing to subunits of RNA polymerase I and III. A reduction in functional polymerase I and III results in inadequate quantities of mature ribosomes in the neuroepithelium and neural crest cells leading to activation of cell death pathways and subsequent hypoplasias.[10]

Clinical features

TCS has a broad phenotypic variability, varying from very mild (mostly periorbital soft tissue) deformities which might be hard to detect for clinicians not particularly familiar with these condition, to severe deformities like colobomata of the lower eyelids, refractive errors, down slanting of the palpebral fissures, malar hypoplasia, microtia, middle ear deformities, choanal atresia, palatal cleft and mandibular hypoplasia (Figure 3).[1, 17]

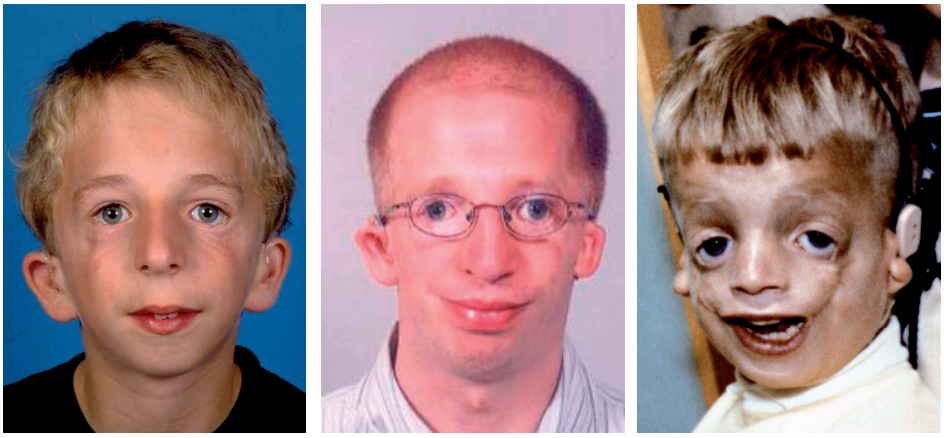

Figure 3. Variable expression of the phenotypic clinical features of Treacher Collins syndrome ranging from mild to more severe (left to right).

Even a case with arhinia and anotia is described.[18] Until now there are no correlations found between the genetic cause and the severity of the phenotypic clinical features. It is assumed that men and women are affected equally.

Prenatal diagnosis

Mid-trimester prenatal diagnosis is possible through a two-dimensional or three-dimensional ultrasonography identifying the presence of for example micrognathia and low-set ears.[19-20] However, one can suppose that very mild forms of TCS might be undetected during regular ultrasonography screening.

Grading systems

Two subjective grading systems have been described until now to grade TCS. Hayashi et al described a scoring system with eight criteria and each criteria was assigned several categories.[21] The eight criteria are: deformity of the malar bone, deformity of the lower eyelid, deformity of the mandible, deformity of the ear, palatal cleft, nasal root, other deformities and the presence of a *TCOF1* mutation. The second is the O.M.E.N.S. classification, as initially proposed for craniofacial microsomia. The acronym indicates five major features: orbital distortion, mandibular hypoplasia, ear anomaly, nerve involvement and soft tissue involvement.[22] Although these classification systems illustrate the variety and severity of the deformities, these classifications have never resulted in any structured (surgical) approach or treatment; therefore they are rarely used in clinical practice.

CLINICAL IMPLICATIONS OF TREACHER COLLINS SYNDROME

Upper airway

TCS is mostly known for the esthetic sequelae, however, functional problems are considered a major issue as well. A known condition which may be present in craniofacial syndromes in general, is obstructive sleep apnea (OSA). OSA is characterized by breathing cessation (apneas) or reduction (hypopneas) as a result of complete or partial upper airway obstruction. The gold standard for diagnosis of OSA is the poly(somno)graphy used in hospital settings or ambulatory measurements at home. For screening on OSA alternative tools might be used for the diagnosis but cannot substitute polysomnography.[23] They may be used in low resource settings. Two questionnaires are frequently used in children and adults; in children the Brouillette score (validated in children) and in adults the Epworth Sleepiness scale (validated in adults).[24-26] However, the Brouillette score has a poor sensitivity and specificity for the prediction of polysomnography results.[23] Based on the current literature, the prevalence of OSA in TCS is estimated between 25- 95%.[27-28] In for example syndromic craniosynostosis the prevalence of OSA is determined to be 68%.[29] In that patient category, the Brouillette score could not differentiate between OSA and non OSA.[30] Also in TCS it is unknown whether questionnaires are accurate for the diagnosis OSA.

The mechanism underlying OSA in TCS is attributed to mandibular hypoplasia together with a posterior tongue collapse. This can narrow the upper airway at the level of the oro/hypopharynx significantly resulting in sometimes severe OSA. However, instead of an one level origin, some studies report obstructions at more than one level.[28, 31-33] Airway problems can be so severe that they can result in peri- or postnatal early death through fatal airway compromise. In children with OSA there might be an increased prevalence of abnormalities which reflect associated morbidity**.** Central nervous or cardiovascular system morbidity, growth failure or enuresis should be recognised. Central nervous abnormalities include excessive daytime sleepiness, increased frequency of inattention/hyperactivity symptoms, increased prevalence of cognitive deficits and increased frequency of behavioral disorders.[34-35] Morbidity from the cardiovascular system may be reflected in elevated blood, increased risk of pulmonary hypertension and cor pulmonale. Moreover, OSA is associated with oxidative stress and systemic inflammation.[36] Cytokines are released including interleukin 1, interleukin 6, tumor necrosis factor α and C-reactive protein. These proinflammatory proteins can induce oxidative stress, systemic inflammation and sleepiness.[37-41] Through these pathways OSA can lead to atherosclerosis and vascular dysfunction.[42] So far these comorbidities in the cardiovascular system have not been described in children and adults with craniofacial syndromes.

The ear, hearing and speech

Around 93-96% of the TCS patients suffer from a certain degree of unilateral or bilateral conductive hearing loss.[43-45] In addition, around 50% suffer from a certain degree of communication problem.[46] A variety of complex middle ear deformities (hypoplastic, ankylosed or missing ossicles) contribute to a conductive hearing loss. Hypoplasia of the mastoid and mastoid antrum, absence of the external auditory canal or even absence of the middle ear and epitympanic space are noted and could further impede conductive hearing. There are limited options for surgical reconstruction. However, hearing rehabilitation through a bone anchored hearing aid is an option for these patients.[43, 47-49] There is limited evidence for patients' experience of success of hearing rehabilitation. The inner ear is assumed to be usually normal.[50] The degree of hearing impairment may correlate with the external ear deformity as scored with the auricle four category system of craniofacial microsomia.[45, 51] This suggests that a correlation exists between the severity of the deformity of the pinna and external auditory canal and the middle ear deformities.

The eye, eyelashes and lacrimal system

Periorbital soft tissue defects are one of the cardinal facial features of TCS. The identifiable "down slanting" of the eyelids are almost always present. Although the syndrome was named after an ophthalmologist, (intra-)ocular deformations are seldom mentioned. An assortment of ocular conditions can be found in TCS: vision loss (37%), amblyopia (33%),

significant refractive errors (58-86%), anisometropia, bilateral absence of the inferior lacrimal puncta (36%) or cilia (50%), regular astigmatism (36%) and absent lateral canthal tendon (64%).[17, 52] In addition, corneal drying through colobomata can give irritation of the globe. Regarding these topics very limited evidence can be found in literature.

Growth, feeding and swallowing

In craniofacial syndromes feeding difficulties and growth failure are described which are often related to OSA. In TCS, also swallowing dysfunctioning can occur.[46] Patients reported eating difficulties up to 68% and dry mucosa in 42%.[46] A reduced jaw opening (63%), malocclusion (94%) and a narrow hypopharynx are the basis of the anatomic limited normal feeding route.[46] Dysplasia and even aplasia of the parotid gland can occur with or without a detectable orifice of Stenson's duct.[53] It is unknown how often these functional impairments lead to growth failure in TCS.

The nose

On the level of the midface, one of the less prominent deformities can be found: the nose. Current treatment overviews seldom describe nasal reconstruction or considerations of other (endonasal) treatment of the nose.[11, 45, 54-55] However, it is known that choanal atresia occurs now and then in TCS.[45] This can cause significant nasal obstruction. The external nose can be deformed as well. Although the height and width are mostly optimal, the nose is often protruded proximally with a wide nasal root.[56] Moreover, the clinical picture suggests a dorsal hump deformity.[11, 45, 54-55] Evidence considering reconstructive nasal surgery or patients' experience is currently lacking.

Psychosocial factors

The effect of the congenital craniofacial anomalies of TCS patients on their psychosocial functioning, has not been investigated well.[57] It is known that stress and avoidance behavior can be elicited by stigmatization and insecurity about experiencing negative reactions of others.[58-59] In addition patients with congenital facial deformities may have an impeded social functioning.[60-61] The exact coping mechanisms or long-term psychological functioning, however, is unknown in TCS. No recent studies suggest a lower average level of intelligence in TCS patients, compared to the normal population. Concerning self-esteem only in one study it was shown that surgical improvements of facial appearance may have positive influence on self-esteem and adaptive functioning in TCS on the short-term postoperatively.[62]

Craniofacial reconstruction and the multidisciplinary approach

Since it's multidisciplinary character of the syndrome various specialists should be involved in the diagnosis and treatment. Plastic and reconstructive surgeons, oral- and

maxillofacial surgeons, clinical geneticist, pediatricians and otorhinolaryngologists are involved to a certain extent. The rarity of the syndrome together with the variety of the phenotypic expression makes the multidisciplinary staged surgical treatment complicated. No "standard" procedure or protocol exists. Many ways of surgical reconstruction have been published by experts in craniofacial surgery; they published mainly their own experience and opinions.[45, 54-55, 63-68] Generally, the main targets are the periorbital soft tissue, hypoplastic maxilla and mandible. Options for zygoma, orbital floor and lower rim are free grafts or pedicled flaps.[69-70] Techniques described for correcting midface hypoplasia are the Le Fort I and II, rib grafts, malar osteotomies with or without onlay grafts or lipofilling.[66, 71-72] The retrognatic mandible is often distracted for esthetic and functional indications, for example to overcome severe airway compromise and/or tracheotomy and to ameliorate feeding.[73-75]

OUTLINE AND AIMS OF THE THESIS

The range of functional and esthetic problems patients with TCS exhibit during life, the diversity of (and multiple stage) surgeries and psychological sequelae may be extensive. In contrast, craniofacial research is limited and with low levels of evidence. The limited research is probably due to the rarity, the relatively "low impact" these craniofacial syndromes have in our society and lack of centralization of these conditions in craniofacial centers.

Even for relatively "severe" conditions like OSA very limited evidence has been provided for its' exact occurrence and cause in TCS. Although it is known that OSA occurs in TCS, until now, the exact prevalence, cause and severity of OSA have been unknown; therefore we try to determine these entities in **chapter II** of the thesis.

Alternatives for polysomnography to diagnose OSA in TCS patients may be the use of a specific questionnaire for children and adults, which are discussed in **chapter III.**

As OSA is associated with oxidative stress and systemic inflammation, this may introduce cardiovascular disease. In a group of children and adults with craniofacial anomalies and with and without OSA (including patients with TCS) parameters of oxidative stress and inflammation were investigated and described in **chapter IV**.

Multiple craniofacial surgeries at a relatively young age are performed in TCS. One of the main goals for surgery is satisfaction with facial appearance. But how does the surgical treatment succeed for specific facial features and functioning of the face on the long term? Are patients satisfied in the end? Is there still a wish for further treatment? The deficits of facial functions and esthetics as experienced by TCS patients compared with controls are discussed in **chapter V**.

It may be plausible that patients with congenital craniofacial deformities can experience psychological issues, which alter or impede daily functioning. **Chapter VI** assesses the impact of congenital craniofacial deformities on the long-term psychological functioning. Satisfaction with facial appearance, objective severity, fear of negative appearance evaluation and self-esteem are compared with a control group and a group with a traumatically acquired facial deformity.

In **chapter VII** a relatively unknown feature of TCS is investigated into more extent, the nose. Clinical picture suggested a beaked nose and a possible cause of OSA might be present at the level of the nose. Moreover, as less attention has been paid to the nose, it is questionable whether TCS patients are indeed satisfied with functions and esthetics of the nose? Therefore, external and endonasal deformity and satisfaction with nasal functioning and appearance are determined in TCS.

No reviews or guidelines are available on evidence-based treatment for the multidisciplinary approach in TCS. In order to provide a basis for future research and to assist physicians in their clinical decision-making **Chapter VIII** (i.e. also the **general discussion** of the thesis) aimed to provide an evidence-based review of multidisciplinary treatment of TCS based on levels of evidence and supported with graded recommendations.

In conclusion, this thesis aims to answer four clinical questions in TCS:

1) To determine the prevalence, severity, cause and screening of OSA and potential effects of OSA on oxidative stress and inflammation (chapter II, III and IV)
2) To determine which facial features, functions and psychosocial aspects need more attention during surgical treatment on the long-term (chapter V and VI)
3) To determine external and endonasal deformity, and satisfaction with nasal functioning and appearance (Chapter VII)
4) To provide an evidence-based review of multi-disciplinary treatment of TCS based on levels of evidence and supported with graded recommendations (Chapter VIII)

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OBSTRUCTIVE SLEEP APNEA

Chapter II

Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity and cause

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ABSTRACT

This cohort study in 35 patients (13 children) evaluates the prevalence, severity and anatomical cause of obstructive sleep apnea syndrome (OSAS) in patients with Treacher Collins syndrome.

Ambulatory polysomnography was performed cross-sectionally to determine OSAS prevalence and severity. All upper airway related surgical interventions were evaluated retrospectively. In 11 patients, sleep endoscopy, and flexible and rigid endoscopy were applied to determine the level of anatomical obstruction of the upper airway.

The overall prevalence of OSAS in Treacher Collins patients was 46% (54% in children and 41% in adults). Thirty-eight upper airway related surgical interventions were performed in 17 patients. Examination of the upper airway revealed various anatomical levels of obstruction, from the nasal septum to the trachea. Most significant obstruction was found at the level of the oro/hypopharynx.

OSAS in Treacher Collins patients is an important problem so all patients should be screened for OSAS by polysomnography. Endoscopy of the upper airway was helpful in determining the level of obstruction. Surgical treatment at one level will not resolve OSAS in most patients because OSAS in Treacher Collins has a multilevel origin. Non-invasive ventilation (continuous positive airway pressure or bilevel positive airway pressure) or tracheotomy should be considered as treatment a modality.

INTRODUCTION

Treacher Collins syndrome (TCS) is a rare congenital craniofacial condition. Its deformities can range from a slight defect of the cilia to severe defects such as micrognatia and zygomaticotemporomaxillary dysostosis. Mandibular hypoplasia, choanal atresia, underdevelopment of the auricles, a downslant of the eyelids, coloboma of the eyelids and hypoplasia of the zygomatic bone and lateral orbital wall are common features of this condition.[1] TCS is an autosomal dominant disorder with an incidence of 1 in 50,000 live births. In more than 60% of cases there is no previous family history and the condition is thought to arise as the result of a *de novo* mutation. TCS is mainly caused by mutations in the *TCOF1* gene, located on chromosome 5, which encodes a low complexity, serine/alanine-rich, nucleolar phosphoprotein known as treacle. Deletions, insertions, splicing, and missense and nonsense mutations in the *TCOF1* gene cause TCS, however alterations in the *POLR1D* and *POLR1C* genes have been demonstrated to cause TCS.[2] Patients with craniofacial syndromes, such as Pierre Robin sequence, Apert, Crouzon and Pfeiffer syndrome, frequently suffer from obstructive sleep apnea syndrome (OSAS).[3-4]

The main factors that lead to OSAS in craniofacial syndromes appear to be midface and/or mandibular hypoplasia. Mandibular hypoplasia may result in a posterior collapse of the tongue base and a decreased oropharyngeal airway.[5] Leaving OSAS untreated may result in major physical and functional impairment due to the disturbed sleep patterns. TCS is a syndrome in which mandibular hypoplasia is a frequent finding, but only a few studies suggest that TCS may be accompanied by sleep apnea.[6-10] All these latter studies are case reports, with the exception of the study by Sher et al. published in 1986.[10] These authors found a prevalence of 25% in a small group of TCS patients using OSAS criteria that differ from the current standards; they did not differentiate between paediatric and adult TCS patients.

It is important to establish the prevalence and severity of OSAS in TCS patients because of its potential long-term physical and functional effects; but this knowledge is currently lacking. The present study determined these factors in a large group of TCS patients, taking into account all respiratory related interventions that these patients had undergone.

MATERIALS AND METHODS

This cohort study comprised a cross-sectional and a retrospective parts and was conducted in a population diagnosed with TCS and treated by the multidisciplinary craniofacial team of the Erasmus MC since 1975 (over 36-years). All patients were eligible for

inclusion if they were diagnosed with TCS within that period. The research protocol was approved by the Ethical Committee of the Erasmus MC (MEC-2008-402).

Patients were contacted by mail or approached personally at a regular appointment in our outpatient clinic. They had to decide whether to participate within month. Patients were contacted at home by telephone if they had not responded to the mail within that period.

Between January 2007 and November 2009 all included patients underwent a nightly ambulatory polysomnography (PSG) for clinical and/or research purposes. Patients were divided into a paediatric group and an adult group based on their age at the time of the PSG; there was no overlap between the two groups. With the use of a paediatric and an adult group (cutoff at age ≥18 years) the authors were able to determine the proportion of patients suffering from OSAS in both groups separately. PSG was carried out with the Embletta Portable Diagnostic System and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland).[11] Cardiorespiratory variables were measured in the clinical or home setting. Respiratory variables measured were nasal airflow, chest and abdominal wall motion, snoring, oxygen saturation, and oximeter pulse waveform. The minimal total registration time was 6 hours. Analysis of the PSG was expressed in the apnea-hypopnea index (AHI) and the oxygenation-desaturation index (ODI). AHI was defined by the number of obstructive apneas and hypopneas per hour. ODI was defined by the number of desaturations (≥ 4% decrease with respect to the baseline oxygen saturation during 10 s) per hour. An obstructive apnea was defined as a cessation of airflow referred to baseline airflow signal, during at least 10 s or less if followed by desaturation. A hypopnea was defined as a reduction in airflow of 50% referred to baseline airflow signal, during at least 10 s or less if followed by desaturation.

For children the *obstructive*-AHI (OAHI) was used. Central apneas were not included. An OAHI score <1 was considered to be normal for children, 1-5 was defined as mild OSAS, 5-24 as moderate OSAS, and a score >24 as severe OSAS.[12-13] The duration of obstructive apnea and hypopnea was defined as "longer than two breaths".[11] ODI scores were taken into account, but not for diagnostic differentiation between grades of severity of OSAS in children.

For adults, the current OSAS guideline standards for adults were used.[14-15] OSAS was diagnosed when AHI fell outside the normal limit (AHI >5). An AHI of 5-15 was defined as mild OSAS, 15-30 as moderate OSAS, and an AHI > 30 was defined as severe OSAS.

Regarding upper airway surgery, a retrospective chart review was performed on upper-airway-related surgery in all patients. Surgery performed in other medical centers was also taken into account. All available PSGs and presence of a tracheotomy or use of continuous positive airway pressure (CPAP) for severe OSAS were taken into account. Types of surgeries were categorized according to the level of the upper airway.

Regarding sleep endoscopy and level of obstruction in TCS with OSAS, data on drug-induced sleep endoscopy were taken into account for patients suffering from severe OSAS to assess the anatomical site of obstruction during sleep. The jaw-thrust maneuver was applied to check whether the obstruction could be alleviated. If available, results from flexible and rigid endoscopy were taken into account. Plain lateral skull radiographs for cephalometric analysis were taken to determine the severity of the mandibular/maxillary hypoplasia.

Statistical analysis

All statistics concern descriptive numerical and categorical data. Measured values are reported as mean ± 1 standard deviation (SD) or median (range), as appropriate. Outcomes of PSGs are expressed as median and interquartile range. Analyses were made using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Population

From 1974 through 2010, 58 patients were diagnosed with TCS. In this period four patients died: three suffered from severe OSAS, two deaths were not related to OSAS, and the cause of death was unknown for one patient. The death of one patient was related to OSAS because of asphyxiation due to frequent aspiration. Of the 54 patients, 19 did not participate due to emigration (one patient), lack of correct personal details (three patients), unwillingness to participate (14 patients), and loss to follow-up (one patient). At least two patients who refused to participate suffered from severe OSAS (one tracheotomy, and one used CPAP). Another patient who was lost to follow-up was known to have a tracheotomy for severe OSAS.

Thirty-five of the 54 patients (65%) were included in this study. At time of the inclusion this group comprised 13 children (five boys) and 22 adults (10 males). Median age of the paediatric group was 12 years (range 0-17 years) and for the adult group, 37 years (range 20-60 years). The median body mass index of the adult group was 20.7 (15.2-29.4), and was 17.4 (11.0-20.5) in the paediatric group.

Polysomnography

A PSG was performed in 12 children and showed OSAS in six of them. No PSG was performed in one child who required instant treatment (tracheotomy) for severe OSAS; because temporary closure of the cannula caused immediate breathing problems, decannulation was impossible. This patient was therefore classified as having severe OSAS without undergoing a formal assessment. Seven of the 13 children (54%) had

OSAS: one mild, five moderate and one severe (Table 1). Five of the 13 children (38%) had undergone airway treatment prior to these measurements.

A PSG was performed in all 22 adults; OSAS was diagnosed in nine (41%). Mild OSAS was diagnosed in three patients and severe OSAS in six patients (Table 1). Of these 22 adults, 12 had undergone airway treatment (55%) prior to these measurements.

Table 1. Cross-sectional polysomnography outcomes in paediatric and adult TCS patients (n=35)

Prevalence	No OSAS	Mild OSAS	Moderate OSAS	Severe OSAS	Total
TCS children (n=13)	46% (6/13)	8% (1/13)	38% (5/13)	8% (1/13)*	54% (7/13)**
Median OAHI (interquartile range)	n/a	0.9 (-)	5.4 (5.2-11.0)	-	
Median ODI (interquartile range)	n/a	1.9 (-)	8.3 (0.3-20.2)	-	
TCS adults (n=22)	59% (13/22)	14% (3/22)	0% (0/22)	27% (6/22)	41% (9/22)**
Median AHI (interquartile range)	n/a	9.0 (9.0-14.0)	-	55.0 (54.0-111)	
Median ODI (interquartile range)	n/a	4.0 (2.0-6.0)	-	28.5 (14.5-38.75)	
Total (n=35)	54% (19/35)	11% (4/35)	14% (5/35)	20% (7/35)	46% (16/35)**

n/a = not applicable

*No PSG was performed in one child who required instant treatment (tracheotomy) for severe OSAS. Because temporary closure of the cannula immediately caused severe breathing problems this patient was classified as having severe OSAS, without undergoing formal assessment.

**Twelve of the 22 adults and 5 of the 13 children underwent airway surgery prior to the PSG.

Upper airway surgical procedures in TCS

In 17 (49%) of the 35 TCS patients 38 interventions related to the upper airway were performed. Figure 1 shows the schematic follow-up process.

A tracheotomy was performed in two of the newborn infants because of severe upper airway obstruction. One of these patients has now reached adulthood and has been successfully decannulated.

Nasal surgery was performed in three patients (two in childhood) aged five, 17 and 49 years at the time of intervention. Two patients suffered from severe OSAS preoperatively. In the adult patient the distinct septum deviation was surgically corrected, resulting in a reduction of apneas of 224 to 3 per/h during the night (Fig. 1: no.7) (Table 2: no.7). In one paediatric patient (with severe OSAS preoperatively), surgery for choanal atresia at five years of age resulted in moderate OSAS postoperatively.

Maxillary surgery was performed in seven patients (six in childhood): age range 15-20 years at time of intervention. In five patients a Le Fort I osteotomy advancement was performed, in one patient with internal distraction. Preoperatively, three patients were diagnosed with severe OSAS and two of them showed no OSAS after a Le Fort I procedure. Indications for Le Fort I procedure were improvement of occlusion and orthognathic correction following mandibular surgery. A surgically assisted rapid maxillary expansion

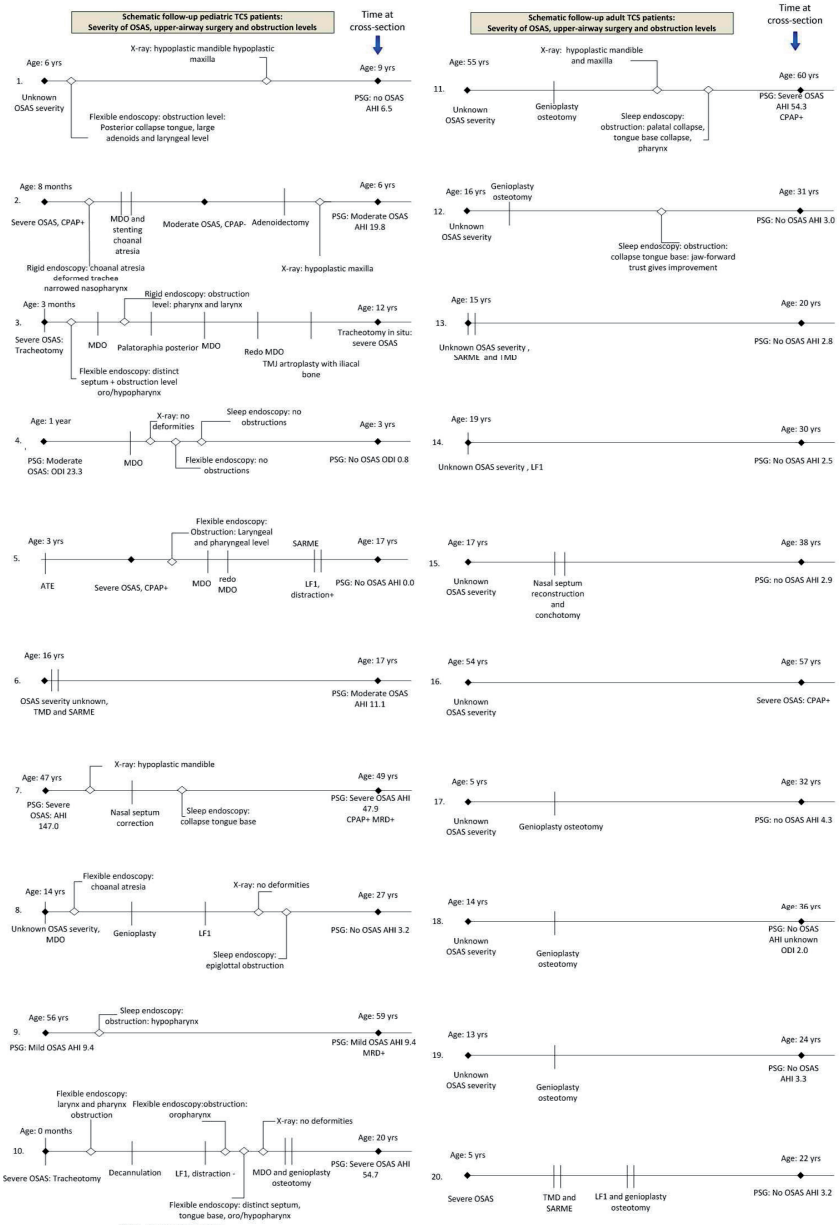

Figure 1. Schematic follow-up of TCS patients: time at polysomnography, severity of OSAS, all forms of invasive or non-invasive airway treatment, endoscopies and X-rays are presented together with the obstruction levels.

Symbols used:

- ◆ OSAS diagnostic evaluation moment
- | Surgical intervention
- ◇ Obstruction level evaluation moment

Abbreviations:

MDO: Mandibular distraction osteogenesis
MRD: Mandibular repositioning device
PSG: Polysomnography
SARME: Surgically assisted rapid maxillary expansion
TMD: Transmandibular distractor

Table 2. Levels of obstruction found in the upper respiratory tract in 10 patients with Treacher Collins syndrome

Levels of obstruction in the upper respiratory tract including the diagnostic tools used including the diagnostic tools used										
	Paediatric cases					Adult cases				
Level of obstruction	No.1	No. 2	No. 3	No. 5	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12
Nasopharynx										
Choana		Rigid				Flex				
Septum			Flex					Flex		
Nasopharynx*		Rigid								
Maxilla	X-ray	X-ray							X-ray	
Adenoid	Flex									
Oropharynx										
Palate									Sleep	
Oro/hypopharynx			Flex				Sleep	Flex		
Glossoptosis	Flex				Sleep				Sleep	Sleep
Hypoplastic mandible	X-ray				X-ray				X-ray	
Laryngopharynx										
Pharynx*			Rigid	Flex				Flex	Sleep	
Epiglottis						Sleep				
Larynx	Flex		Rigid	Flex				Flex		
Trachea		Rigid								

* not further specified

Case numbers correspond with figure 1. Only detected levels of obstruction are reported. Case no. 4 had no upper airway obstruction on endoscopy.

X-ray = cephalometric X-ray; Flex = flexible endoscopy; Slee*P* = sleep endoscopy; Rigid = rigid endoscopy.

(SARME) was performed in four of seven patients (two in childhood), combined with a Le Fort I in two patients.

In eight patients (two in childhood) a genioplasty was performed. Three of these eight patients suffered from severe OSAS: age range 13-56 years at time of intervention. A genioplasty was the only surgical intervention applied in five patients to correct mandibular hypoplasia. Three of these eight patients suffered from severe OSAS. The genioplasty did not result in a reduction of OSAS severity in any of the patients.

In six patients (five in childhood) a mandibular distraction osteogenesis was performed for their micrognatia: age range 1-20 years at time of intervention. Preoperatively, four patients suffered from severe OSAS, one from moderate OSAS and one was unknown. Postoperatively, two patients still suffered from severe OSAS, one patient from moderate OSAS and three showed no OSAS. The patient with preoperative moderate OSAS showed no obstructions postoperatively (Fig. 1 no. 4). In two of the three patients the

postoperative absence of OSAS was not attributable solely to the mandibular surgery because a Le Fort I was also performed, in one child following a SARME.

In three patients (all in childhood) a transversal mandibular distraction osteogenesis was performed: age range 15-17 years at time of intervention. These procedures were combined with a SARME. Preoperatively, two patients suffered from severe OSAS which resolved after surgery. Postoperative OSAS results were not attributable solely to these interventions, because a SARME was also performed in these two patients.

In one patient an adenoidectomy was performed at five years of age, and in another patient an adenotonsillectomy was performed at three years of age. Both patients suffered from severe OSAS and used CPAP. Postoperatively, one had no OSAS and one had moderate OSAS (AHI 19.8). Postoperative OSAS results were not attributable solely to this intervention, because a mandibular distraction osteogenesis was also performed in these two patients.

Endoscopy of the upper airway was performed in 11 patients: sleep endoscopy in six (age range 3-60 years, five in adulthood), flexible endoscopy in six (age range 3-19 years, one in adulthood), and rigid endoscopy in two patients (both in childhood, age range 0-9 years). In seven of 11 patients cephalometric X-rays were analysed. Upper airway obstructions were found in 10 of the 11 patients. Table 2 presents the results of these investigations (only detected obstruction levels are reported).

DISCUSSION

This cohort study shows that OSAS is frequently present in patients with TCS. The prevalence of OSAS was 41% in adults and 54% in paediatric patients. The overall prevalence of OSAS (46%) is high compared with the prevalence in healthy children and adults, but almost the same as in patients with syndromic craniosynostosis.[16] The present population tends to be more prone to severe OSAS (20% overall prevalence of severe OSAS) compared with severe OSAS in syndromic craniosynostosis (4-12.5%).[4, 11, 17-20] Remarkably, in four of six adults diagnosed with severe OSAS, OSAS was not recognized as such prior to this study. There may have been a discrepancy between the severity of airway obstruction and complaints may have existed in these patients, which might have led to underdetection of OSAS. Bearing in mind that 38% of the children and 55% of the adults had undergone upper airway related surgery at the time of the cross-sectional measurement, this probably resulted in an underestimation of the initial prevalence and severity. Despite these surgeries this study shows that the proportion of patients suffering from OSAS is high and similar in children and adults.

Endoscopy showed various levels of obstruction from nose to trachea, including obstruction due to the nasal septum and choanal atresia, obstruction at the maxilla,

narrowing at the level of the nasopharynx/laryngopharynx, posterior collapse of the tongue base, and tracheal malformation. In almost all patients a combination of one of these levels of obstruction was found.

One study reported pharyngeal narrowing in all 11 TCS patients using endoscopy; in most of these patients narrowing was throughout the entire vertical pharyngeal height.[21] In that study, the authors found a typically anteroinferiorly displaced hyoid bone. In addition to the present results, these findings imply that OSAS has a complex multiple level origin in TCS. Overall there is a contrast with syndromic craniosynostosis, in which midface hypoplasia with collapse of the pharyngeal wall and obstructions at the level of the nasopharynx are generally considered to be the major cause of obstruction.[19]

Treatment of OSAS at one level may not resolve OSAS because OSAS is caused by obstruction at multiple levels. In this study, OSAS persisted in two patients after extensive surgical airway treatment (Fig. 1, case nos. 3 and 10), and improved dramatically in two (case nos. 2 and 4). Concerning surgery at the nasopharynx level in TCS patients, it is useful to examine the nasal cavity because nasal surgery can reduce the airway obstruction.[22-23] This is shown by one of present patients (Fig. 1 case no. 7): a nasal septum correction caused a significant reduction in OSAS. In the authors' opinion, the value of a genioplasty to improve airway obstruction remains doubtful, given the disappointing results in three patients (Fig. 1 case nos. 10, 11, 20).

The authors hypothesise that maxillary advancement (Le Fort I) may be indicated. In two cases (Fig. 1 case nos. 5 and 20) this intervention seemed to resolve OSAS completely, but there are no reliable pre- and postoperative PSG data to prove it.

Most interventions can be effective in resolving airway obstruction, but may fail in TCS due to its multilevel origin in these patients. Therefore, prior to surgical treatment of OSAS, the exact levels of obstruction need to be taken into consideration.

A limitation of this study is that determination of the level of obstruction was not standardized; different ways of endoscopy were used, sometimes retrospectively. We did not use 3D CT scans to measure airway volumes, although this would have allowed more precise measurement.

In most patients the preoperative severity of OSAS is unknown. Therefore, our conclusions with regard to surgical treatment were limited to the cases in which preoperative and postoperative OSAS severities were known.

This cross-sectional cohort study shows that OSAS in TCS patients is an important problem in childhood and adulthood. Owing to the potential long-term untreated effects of OSAS all new TCS patients need to be screened for OSAS with PSG. The authors suggest annual screening for OSAS during the first few years of life. Endoscopy of the upper airway is helpful to determine the level of obstruction. Because OSAS in TCS has a multilevel origin, in most of the patients surgical treatment at one level is unlikely to

resolve OSAS. Therefore non-invasive ventilation, such as CPAP or bilevel positive airway pressure or a tracheotomy should be considered as treatment modality.

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Chapter III

Screening for obstructive sleep apnea in Treacher Collins syndrome

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ABSTRACT

Objectives/Hypothesis This study evaluated the accuracy of established obstructive sleep apnea syndrome (OSAS) questionnaires based on presenting symptoms and complaints as screening tools for OSAS in Treacher Collins syndrome (TCS).

Study design Cross-sectional cohort study.

Methods In 35 TCS patients (13 children, 22 adults) in whom diagnostic polysomnographic results on OSAS were available, the Brouillette score was evaluated in children and the Epworth Sleepiness Scale in adults.

Results The total Brouillette score showed a sensitivity of 50%, specificity of 71%, positive and negative predictive value of 60% and 63%, respectively. The answer "no" to the question whether a child snored could rule out OSAS in children and showed positive and negative predictive values of 55% and 100%, respectively.

The Epworth Sleepiness Scale showed a sensitivity of 0%, specificity of 92%, positive and negative predictive values of 0% and 57%, respectively. A positive answer to the question of whether a person falls asleep while sitting and talking to someone (sometimes or more) was able to predict OSAS in adults. This question showed positive and negative predictive values of 100% and 72%, respectively.

Conclusions This cross-sectional cohort study shows that the Brouillette score and the Epworth Sleepiness Scale are of minimal usefulness in TCS. Diagnosis of OSAS based solely on complaints is not reliable, probably due to habituation. Therefore, for a good evaluation and optimal multidisciplinary treatment of this chronic disease in TCS, all newly referred pediatric and adult TCS patients should be screened for OSAS at least once with a polysomnography.

INTRODUCTION

Treacher Collins syndrome (TCS) is a rare congenital craniofacial syndrome. Deformities can range from minor defects in the periorbital region to a full clinical presentation which is characterized by defects such as mandibular hypoplasia and hypoplasia/aplasia of zygoma, microtia and middle-ear deformities.[1] TCS is an autosomal dominant disorder of craniofacial development with an incidence of 1 in 50,000 live births.[2] In more than 60% of cases there is no previous family history and the condition is thought to arise as the result of a *de novo* mutation. Loss-of-function mutations are generally found in the *TCOF1* gene; however alterations in the *POLR1D* and *POLR1C* genes have been demonstrated to cause TCS as well.[3-4]

Patients with craniofacial syndromes frequently suffer from obstructive sleep apnea syndrome (OSAS). OSAS is characterized by breathing cessation (apneas) or reduction (hypopneas) as a result of complete or partial upper airway obstruction. This disorder is one of the most frequent forms of sleep-disordered breathing, associated with major physical and functional impairment due to the disturbed sleep patterns.[5] OSAS is a frequent finding in TCS.[6-9] Severities range from mild to severe in pediatric and adult TCS patients, of which a considerable number suffered from severe OSAS.

Definitive diagnosis and grading of OSAS requires polysomnography (PSG), which is considered the gold standard for diagnosis. Normally, diagnosis is often supported by symptoms like snoring and excessive sleepiness in adults.[10-11] In children, symptoms can be apneas, snoring and increased respiratory effort which can lead to failure to thrive, recurrent respiratory infections, feeding difficulties, and disturbed cognitive functions such as attention deficit and impaired concentration and memory.[12] However, symptoms as presented often remain unrecognized in patients with OSAS.[13]

Because the presence of symptoms/complaints in a normal population can be suggestive for OSAS and supports the diagnosis, it is important to know whether it is possible to predict OSAS in patients with TCS with two validated questionnaires used for screening for OSAS.[11, 14-16] Currently, no scientific evidence is available regarding screening for OSAS in TCS either with PSG or validated questionnaires. Given the high prevalence of OSAS in TCS, it is essential to clarify whether symptoms/complaints of OSAS are of diagnostic value.

Therefore, the present study aimed to: 1) determine whether it is possible to predict OSAS with two validated OSAS questionnaires, 2) explore differences in outcomes of these questionnaires (symptoms), and 3) determine the frequency of different symptoms. To establish this, the same TCS cohort was investigated in which we established the prevalence and severity of OSAS with the gold standard (i.e., PSG).

MATERIALS AND METHODS

Patient selection

We conducted a cross-sectional cohort study to establish the complaints associated with OSAS in a population diagnosed with TCS. Patients were included if they were diagnosed with TCS and treated by the multidisciplinary craniofacial team of the Erasmus MC.

The group was divided into pediatric and adult patients (cutoff at age ≥18 years). The study was approved by the Ethical Committee of the Erasmus MC (MEC-2008-402).

Polysomnography

A clear objective diagnosis of OSAS through PSG was available for 35 TCS patients (13 children, 22 adults) (Table 1). Current guideline standards were used for the diagnosis of OSAS for children according to the consensus.[10, 17-19]

For children the obstructive Apnea-Hypopnea Index (AHI) was used. Central apneas were not included. An obstructive AHI score > 1 was defined as mild OSAS. An AHI ≥ 5 and < 24 was defined as moderate OSAS, and a score ≥ 24 as severe OSAS.

For adults, the diagnosis of OSAS was according to the Adult OSA Task Force of the American Academy of Sleep Medicine.[20-21] OSAS was defined as mild for AHI ≥ 5 and < 15, moderate for AHI ≥ 15 and ≤ 30, and severe for AHI > 30 per hour.

Table 1. Prevalence of obstructive sleep apnea in children and adults with Treacher Collins syndrome (TCS) based on polysomnography (n=35)

	Mild OSAS	Moderate OSAS	Severe OSAS	Total
Prevalence	% (No.)	% (No.)	% (No.)	% (No.)
TCS children (n=13)	8 (1/13)	38 (5/13)	8 (1/13)*	54 (7/13)
TCS adults (n=22)	14 (3/22)	0 (0/22)	27 (6/22)	41 (9/22)
Total (n=35)	11 (4/35)	14 (5/35)	20 (7/35)	46 (16/35)

* One patient received immediate treatment for severe airway obstruction, therefore no polysomnography prior to treatment was available.
OSAS = obstructive sleep apnea syndrome; TCS = Treacher Collins syndrome

Questionnaires

Pediatric questionnaire

Brouillette et al. developed an OSAS score to predict the presence of OSAS with a high sensitivity in normal children. To make a clear inventory of the complaints associated with OSAS in this cohort we used the Brouillette score for pediatric patients.[22] The parents of these children answered the questions.

The Brouillette score is calculated using the following formula: 1.42 D + 1.41 A + 0.71 S – 3.83. Where D stands for difficulty in breathing and S for snoring, using different scores for the frequency of the complaint (never = 0, sometimes = 1, often = 2, always = 3); A

stands for apnea and is scored 0 if apnea does not occur and scored 1 if it does. A Brouillette score below –1 is defined as no OSAS, between –1 and 3.5 as suggestive for OSAS and greater than 3.5 as OSAS.[22]

Children were divided into an OSAS group and a non-OSAS group based on the PSG results.

Adult questionnaire

Daytime sleepiness was assessed using the Epworth Sleepiness Scale. The Epworth Sleepiness Scale provides a rapid and quantifiable assessment of subjective sleepiness as cardinal daily symptom of OSAS.[11, 23] Adults were asked "How likely are you to doze off or fall asleep in the following situations?" in eight different situations. The following situations were described according to the Epworth Sleepiness Scale: 1) sitting and reading, 2) watching television, 3) sitting inactive in a public place (for instance, a theater or meeting), 4) as a passenger in a car for an hour without a break, 5) lying down to rest in the afternoon when circumstances permit, 6) sitting and talking to someone, 7) sitting quietly after a lunch without alcohol, 8) in a car, while stopped for a few minutes in traffic. The total score of the Epworth Sleepiness Scale is the sum of the responses to the eight individual items and ranges from 0 to 24. Values ≥ 10 indicate significant sleepiness and a relation with OSAS and prompts further evaluation; values ≥ 16 indicate a high level of daytime sleepiness. Adults were divided into an OSAS group and a non-OSAS group.

Statistical analysis

Accuracy of the questionnaires was determined by using contingency tables to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of total scores and separate items of the questionnaires, as appropriate. To calculate the above-mentioned values a cutoff ≥ -1 was used (suggestive for OSAS) in the total Brouillette score. A cutoff ≥ 1 was used per question in the Epworth Sleepiness Scale. A cutoff ≥ 10 was used for the total score in this questionnaire.

The unpaired *t* test with equal variances with two-tailed significance was used to compare differences in mean scores in all questionnaires between the OSAS group and the non-OSAS group. The Bonferroni correction for significance for multiple testing was used in all questionnaires. A *P*-value ≤ 0.05 was defined as significant. Analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Population

In the period 1974 through 2010, 58 patients were diagnosed with TCS. Of these four died, and 19 did not participate due to emigration (one patient), lack of correct personal details (three patients), unwillingness to participate (14 patients) and loss to follow-up (one patient). Of the 54 patients, 35 (65%) were included in the present study. Of these 35 patients, 34 underwent PSG. In one patient no PSG was performed due to severe airway problems which necessitated immediate tracheotomy; therefore this patient was considered to have severe OSAS.

All patients filled out the questionnaires on the same day that the PSG was performed. This cohort comprised 13 children (five boys) and 22 adults (10 males). Median age of the pediatric group was 12 years (range, 0-17 years), and median age of the adult group was 37 (range, 20-60 years).

Questionnaires

Pediatric questionnaire

Parents of all 13 pediatric TCS patients filled out the Brouillette score. Although children with OSAS scored higher than children in the non-OSAS group, the difference was not significant (0.42 vs. -1.81, $P = 0.094$) (Table 2). The total Brouillette score showed a low sensitivity (50%), specificity (71%), and a low PPV and NPV (60% and 63%, respectively). The most frequent complaint in children was snoring. PPV of the three separate

Table 2. Brouillette score and separate items as tools for predicting obstructive sleep apnea syndrome in children with Treacher Collins syndrome (n=13)

Brouillette score and separate items OSAS (n=6) Non-OSAS (n=7)	OSAS Mean (SD)	Non-OSAS Mean (SD)	*P* value	Se % (No.)	Sp % (No.)	PPV % (No.)	NPV % (No.)
Difficulty in breathing +	1.33 (1.37)	0.29 (0.49)	-	67 (4/6)	71 (5/7)	67 (4/6)	71 (5/7)
Apnea +	0.67 (0.52)	0.29 (0.49)	-	67 (4/6)	71 (5/7)	67 (4/6)	71 (5/7)
Snoring +	2.00 (0.89)	1.14 (0.90)	-	100 (6/6)	29 (2/7)	55 (6/11)	100 (2/2)
Total Brouillette score > -1	-	-	-	50 (3/6)	71 (5/7)	60 (3/5)	63 (5/8)
Total Brouillette score	0.42 (2.62)	-1.81 (1.76)	0.094	-	-	-	-

OSAS = obstructive sleep apnea syndrome
SD = standard deviation
Se = sensitivity
Sp = specificity
PPV = positive predictive value
NPV = negative predictive value

Table 3. Epworth Sleepiness Scale in adults with Treacher Collins syndrome (n=22): comparison of mean scores, frequency of separate items and tools for predicting obstructive sleep apnea syndrome in Treacher Collins syndrome adults

ESS Items OSAS (n=9) Non-OSAS (n=13)	OSAS Mean (SD)	Non-OSAS Mean (SD)	*P* value	OSAS Frequency scored % (No.)	Non-OSAS Frequency scored % (No.)	Se* % (No.)	Sp* % (No.)	PPV % (No.)	NPV % (No.)
Sitting and reading	0.89 (0.33)	0.85 (1.14)	0.901	89 (8/9)	46 (6/13)	89 (8/9)	54 (7/13)	57 (8/14)	88 (7/8)
Watching television	0.67 (0.71)	1.08 (0.86)	0.253	56 (5/9)	77 (10/13)	56 (5/9)	23 (3/13)	33 (5/15)	43 (3/7)
Sitting inactive in a public place	0.33 (0.71)	0.46 (0.97)	0.738	22 (2/9)	23 (3/13)	22 (2/9)	77 (10/13)	40 (2/5)	59 (10/17)
As a passenger in a car for an hour without a break	0.67 (0.50)	0.31 (0.48)	0.106	67 (6/9)	31 (4/13)	67 (6/9)	69 (9/13)	60 (6/10)	75 (9/12)
Lying down to rest in the afternoon	0.89 (1.05)	1.23 (1.09)	0.473	56 (5/9)	69 (9/13)	56 (5/9)	31 (4/13)	36 (5/14)	50 (4/8)
Sitting and talking to someone	0.44 (0.53)	0.00 (0.00)	0.035	44 (4/9)	0 (0/13)	44 (4/9)	100 (13/13)	100 (4/4)	72 (13/18)
Sitting quietly after a lunch without alcohol	0.11 (0.33)	0.62 (0.65)	0.028	11 (1/9)	54 (7/13)	11 (1/9)	46 (6/13)	13 (1/8)	43 (6/14)
In a car while stopped for a few minutes in traffic	0.22 (0.67)	0.15 (0.38)	0.761	11 (1/9)	26 (2/13)	11 (1/9)	84 (11/13)	33 (1/3)	58 (11/19)
Total ESS score**	4.22 (2.33)	4.69 (3.45)	0.729			0 (0/9)	92 (12/13)	0 (0/1)	57 (12/21)

* Cutoff for sensitivity and specificity for the separate items of the ESS: scores ≥ 1 are used

** Cutoff for sensitivity and specificity for the Total ESS score: scores > 10 are used [23]

OSAS = obstructive sleep apnea syndrome

SD = standard deviation

ESS = Epworth Sleepiness Scale

Se = sensitivity

Sp = specificity

PPV = positive predictive value

NPV = negative predictive value

symptoms as used in this questionnaire ranged from 55% to 67%, of which snoring scored lowest. Specificity of snoring was low (29%) but showed the best NPV (100%).

Adult questionnaire

All 22 adults who underwent a PSG completed the full Epworth Sleepiness Scale. The mean scores of the OSAS and non-OSAS groups on the total Epworth Sleepiness Scale showed no significant difference (4.2 vs. 4.7, $P = 0.729$) (Table 3). The total score of the Epworth Sleepiness Scale showed a sensitivity, PPV and NPV of 0%, 0% and 57%, respectively.

When taking the severe OSAS group separately (as a subset) and comparing the mean total scores of the total Epworth Sleepiness Scale of the severe OSAS group with the non-OSAS group again, no significant difference was found (4.3 vs. 4.7, $P = 0.824$). The question concerning whether a person was falling asleep while sitting and talking to someone showed the best PPV and NPV (100% and 72%, respectively); the score on this question showed a significant difference between the OSAS group and the non-OSAS group (0.4 vs. 0.0, $P = 0.035$). The other question showing a significant difference was sitting quietly after a lunch without alcohol, which was scored higher in the non-OSAS group (0.1 vs. 0.6, $P = 0.028$).

DISCUSSION

The results of this cross-sectional cohort study show that the Epworth Sleepiness Scale and the Brouillette score are not useful in predicting OSAS in adults and children with TCS. The lack of differences between the severity of symptoms/complaints in the OSAS group and the non-OSAS group resulted in low values of sensitivity, PPV and NPV, and of the total scores of these two questionnaires.

Whereas the sensitivity of the Brouillette score in normal healthy children with OSAS is reported to be around 89%, in the present study the sensitivity was very low.[22, 24] This might be because the most frequently scored complaint was snoring in children with TCS. The total score of this screening tool probably failed in our population because nearly all of the children in the present study snored.

Although the snoring question was not specific, the NPV of this question was high (100%) indicating that the answer "yes" to this question was not helpful, whereas the answer "no" was able to rule out OSAS in children.

The fact that almost all children snored is in accordance with a study in children with syndromic craniosynostosis in which 77% of the children reported to snore; therefore, this item could not be used to discriminate between OSAS and non-OSAS.[25] That same study found that asking parents whether the child has difficulty (or not) in breathing

during sleep can exclude the presence of clinically significant OSAS.[25] For this particular question we found a low sensitivity of 67% and an NPV of 71%.

Considering the low predictive values of the total score, the Brouillette score missed around 40% of the OSAS cases in children, based on the cutoff values as used in that score.

Currently, the most widely used self-reporting scale for excessive daytime sleepiness is the Epworth Sleepiness Scale as subjective screening for OSAS in normal healthy patients. However, we found that this scale has no sensitivity and no PPV (both 0%) to detect OSAS. Two items of the Epworth Sleepiness Scale showed a significant difference between the OSAS group and the non-OSAS group. Of these items, the question as to whether a person falls asleep while sitting and talking to someone (sometimes or more) showed the best PPV (100%). Although a positive answer to this question indicates the presence of OSAS, a negative answer did not rule out OSAS. Of all the eight questions, this latter question implies the most extreme daytime sleepiness and suggests hypersomnolence may still be a symptom of OSAS in our population. However, we think this is to a lesser overall degree than expected in a normal OSAS population, because all our total sleepiness scores were relatively low.

Surprisingly, the second significant item falling asleep while sitting quietly after a lunch without alcohol scored significantly higher in the non-OSAS group (showing very low PPV and NPV) and is therefore not useful for screening.

A possible explanation for the fact that the Epworth Sleepiness Scale in adult TCS patients is not discriminative for OSAS is that the patients are accustomed to these symptoms, probably having experienced them from birth. Furthermore, we have to bear in mind that the questionnaires were not filled in due to referral to a specialist because of complaints, but because we requested them to do so.

Limitations

Due to the relatively small study population the results of this study should be interpreted with caution.

CONCLUSION

This cross-sectional cohort study shows that the Epworth Sleepiness Scale and the Brouillette score are of minimal usefulness in TCS. A negative answer to the question snoring can rule out OSAS in children; however, although this question is helpful the PSG is still required as it is the only reliable screening tool. A diagnosis of OSAS based solely on complaints is not reliable, probably due to habituation. Therefore, for a good evaluation and optimal multidisciplinary treatment of this chronic disease in TCS, all

newly referred pediatric and adult TCS patients should be screened for OSAS at least once with PSG.

Future research should focus on the impact on the quality of life of these OSAS-related symptoms/complaints, rather than using these as a screening method for TCS.

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Chapter IV

Is there an effect of obstructive sleep apnea syndrome on oxidative stress and inflammatory parameters in patients with craniofacial anomalies?

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ABSTRACT

This prospective, cross-sectional cohort study included ambulant sleep study data to assess OSAS in patients with syndromic craniosynostosis and Treacher Collins syndrome. Laboratory analyses were performed including malondialdehyde, tumor necrosis factor α (TNF-α) , interleukin 6 and high-sensitivity C-reactive protein.

Forty-eight patients were included; 11 were adults; 37 were children. The patients' body mass indexes were normal, with a median (SD) of 0.7 (-1.82 to 2.48) in children and 20.5 (15.2 – 29.4) in adults. Obstructive sleep apnea syndrome was diagnosed in 23 of 48 patients. It was mild (median obstructive apnea-hypopnea index (oAHI): 2.3; oxygenation-desaturation index (ODI), 0.9) in 16 patients and moderate/severe in sev-enpatients (median oAHI, 10.8; ODI, 5.0). Neither oxidative stress nor inflammation had a correlation with the oAHI and ODI. Only TNF-α was found significantly higher in both the OSAS and non-OSAS groups compared with the reference values (median 15.1 pg/mL and 12.3 pg/mL vs. 4.05 (0.0 - 8.1 pg/mL), $P < 0.001$ and $P < 0.001$, respectively).

Based on our findings we conclude that (mainly mild) OSAS, oxidative stress, as well as high-sensitivity C-reactive protein and interleukin 6 levels are not abnormal in the day time in a population of nonobese patients with a craniofacial anomaly. The increased level of TNF-α cannot be explained by OSAS. Future research should focus on mapping chronobiologic changes for further interpretation of the results.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is highly prevalent in patients with craniofacial anomalies. In most craniofacial anomalies, a genetic cause is known or suspected, including gene mutations in *RUNX2*, *FGFR*, *TWIST*, *ALX3, MSX2* and *TCOF1*.[1-5] This results in for example craniosynostosis and Treacher Collins syndrome, which is associated with a 46% to 72% prevalence of OSAS owing to the anomalies of the development of the face and airway (Figure 1).[6-9]

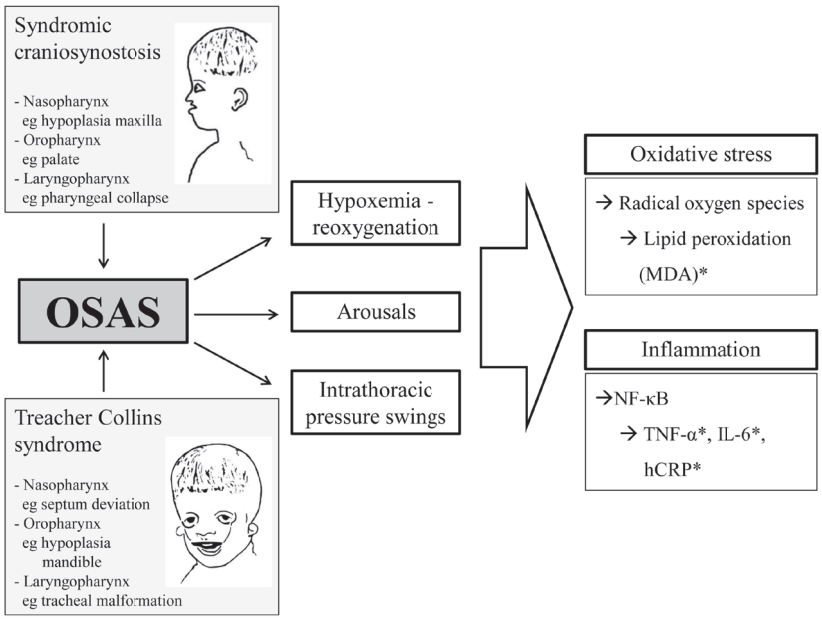

Figure 1: Causes and consequences of obstructive sleep apnea syndrome in craniofacial anomalies.
***** Where MDA = malondialdehyde; TNF-α = tumor necrosis factor alfa; IL-6 = interleukine 6; hCRP = high sensitivity C-reactive protein

OSAS is associated with hypoxia reoxygenation,[10] which resembles ischemia reperfusion. Together with recurrent arousals and changes in thoracic pressure, it may lead to a variety of responses including increased oxidative stress and systemic inflammatory responses.[10-19] Oxidative stress is induced by the production of reactive oxygen species, hydrogen peroxide, and reactive nitrogen species and can be detected by measuring plasma levels of malondialdehyde (MDA) indicating the presence of oxidative stress-induced lipid peroxidation. Consequently, apoptosis of endothelial cells and neurons may occur which induces cardiovascular comorbidity[10, 13] and central nervous system dysfunction.[19] It may also activate inflammatory pathways,[10, 19] for example, by means of

up-regulation of the transcription factor nuclear factor κB.[15] Cytokines are produced and released, including interleukin 1 (IL-1), interleukin 6, tumor necrosis factor α (TNF-α), and acute phase reactants such as C-reactive protein. These proinflammatory proteins can induce oxidative stress, and day-time sleepiness.[13, 18]

Previous research has shown that the levels of oxidative stress and the proinflammatory proteins show a correlation with the severity of OSAS in both adults and children (Figure 1).[12, 14, 16, 18, 20] We are the first to study to what extent OSAS exhibits oxidative stress and inflammation in patients who have a congenital, craniofacial anomaly.

MATERIALS AND METHODS

Participants

A prospective, cross-sectional cohort study was conducted at the Dutch Craniofacial Center from 2007 to 2011. The study was approved by the ethics committee of our institution (METC Erasmus MC MEC-2005-273 and MEC-2008-402). All children with syndromic craniosynostosis and children and adults with Treacher Collins syndrome were diagnosed and/or underwent treatment at the Dutch Craniofacial Center. They were invited to participate by means of written informed consent. Diagnosis of craniosynostosis was based on genetic analysis, including Apert syndrome, Crouzon/Pfeiffer syndrome, Muenke syndrome, and Saethre Chotzen syndrome. If no genetic mutation was found, the patients were classified as having "complex" craniosynostosis. Treacher Collins syndrome was mainly diagnosed clinically. After inclusion of a total of 94 patients, analyses were performed on a fixed number of 48 randomly selected patients (51%).

Sleep study

Overnight sleep respiratory recordings were captured using the Embletta Portable Diagnostic system and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland).[21] The following summary statistics, abnormalities and sleep data were analyzed by visual inspection.[22] Apneas were scored if 80% of flow or greater was reduced during for the length of two breaths in children[22] and for at least 10 seconds in adults. Apneas associated with ≥4% reduction in SpO_2 from baseline were all included regardless of duration in all patients. Hypopnea was identified when flow was reduced 50% or greater in the presence of thoracic and abdominal breathing movement.[23] Hypopneas were only included if a subsequent reduction in SpO2 of 4% or greater from baseline occurred.

The summary statistics from the night sleep study included the apnea-hypopnea index (AHI), where the total number of obstructive as well as central and mixed apneas and pathologic hypopneas were indexed to the duration of sleep (i.e., episodes per hour

of sleep). This statistic was broken down into a combined obstructive and mixed apnea and pathologic hypopnea index (oAHI). A hemoglobin oxygenation-desaturation index (ODI) was calculated as the number of desaturations (≥4% from baseline) per hour of sleep time.

The severity of OSAS in children was graded as mild if the oAHI was 1 or greater and less than 5, moderate if the oAHI was 5 or greater and less than 25, and severe if the oAHI was 25 or greater.[22-24] For adults, OSAS was defined as mild if AHI was 5 or greater and less than 15, moderate if AHI was 15 or greater and 30 or less, and severe if AHI was greater than 30 per hour.[25-26]

Blood samples

Daytime blood samples were collected during surgical procedures related to the craniofacial abnormality in children and at the outpatient department in adults. Laboratory analyses including Malondialdehyde (MDA), Tumor Necrosis Factor alfa (TNF-α), Interleukin 6 (IL-6) and high sensitivity C-reactive protein (hCRP).

1. As a biomarker for oxidative stress malondialdehyde (MDA) was measured in plasma on a Waters Quattro Premier XE® Liquid Chromatography (LC) – Tandem Mass Spectrometry (MS/MS) system.
   - MDA in plasma was first deconjugated by alkaline hydrolysis and subsequently quantitatively analyzed with LC-Electron Spray Ionisation (ESI)-MS/MS, using D2-MDA as an internal standard. The reference range in healthy individuals was 4.6 - 9.4 µmol/L.
2. Inflammatory status was analyzed using TNF-α, IL-6 and hCRP determinations. They were run on the Immulite® Immunoassay System for which serum or heparinised plasma was used.
   - TNF-α was analyzed using an immunometric assay. The range varied from non-detectable to 8.1 pg/mL in healthy individuals and the analytical sensitivity is 1.7 pg/mL.
   - IL-6 was tested with a solid-phase, enzyme-labelled, chemi-luminescent sequential immunometric assay. The range varied from nondetectable to 5.9 pg/mL in healthy individuals and the analytical sensitivity is 2.0 pg/mL.
   - hCRP was analyzed using an immunometric assay. The 97.5th percentile was 11.0 mg/L in healthy individuals and the analytical sensitivity is 0.1 mg/L.

Statistical analysis

Data are presented as median (range). Non parametric statistical tests were applied for all analyses. The Mann-Whitney U test and the one sample Wilcoxon signed rank test were applied for calculating differences between groups and testing of laboratory values against reference values, respectively. The Chi-squared test was used for differences

between gender. Correlations were calculated with the Spearman's test. All tests applied were two-sided and the significance level was set to 5%. Analyses were made in SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 48 patients were included (Table 1). This group consisted of 34 (71%) patients with craniosynostosis and 14 (29%) patients with Treacher Collins syndrome. Eleven were adults, median age 29.2 years (18.6 – 59.2), 37 were children, median age 9.2 years (0.4 - 17.2). OSAS was diagnosed in 23/48 patients. It was mild (median oAHI: 2.3; ODI: 0.9) in 16 patients and moderate/severe in 7 patients (median oAHI: 10.8; ODI: 5.0) (Table 2.). The other patients (25/48, 52%) did not have OSAS (Table 1).

Table 1. Demographic characteristics.

	OSAS (n=23)	Non OSAS (n=25)	Total (n=48)
Diagnosis			
Syndromic craniosynostosis	18	16	34
Apert	5	4	9
Crouzon / Pfeiffer	6	8	14
Muenke	2	1	3
Saethre Chotzen	2	3	5
Complex	3	0	3
Treacher Collins syndrome	5	9	14
Age median (range) yrs	9.8 (0-59)	12.0 (1-50)	11.4 (0-59)
Sex			
Male	10	14	24
Female	13	11	24
BMI			
Children (n = 37)	0.70 (-1.82 - 2.30)	0.67 (-1.10 - 2.48)	0.7 (-1.82 - 2.48)
Adults (n = 11)	21.3 (15.2 - 25.5)	20.0 (15.7 - 29.4)	20.5 (15.2 – 29.4)
Availability laboratory results			
MDA	23/23 (100%)	25/25 (100%)	48/48 (100%)
TNF-α	19/23 (83%)	20/25 (80%)	39/48 (81%)
IL-6	20/23 (87%)	20/25 (80%)	40/48 (83%)
hCRP	19/23 (83%)	20/25 (80%)	39/48 (81%)

Age ($P = 0.14$) and the distribution of sex ($P = 0.39$) was not different between patients with and without obstructive sleep apnea syndrome (OSAS). Body mass index was not different between patients with OSAS and without OSAS (Children $U = 161.5$; Z = -0.29; P-value = 0.78) (Adults $U = 10.0$; Z = -0.11; $P = 1.00$)
Where BMI = Body Mass Index in kg/m^2; MDA = Malondialdehyde; TNF-α = Tumor Necrosis Factor alfa; IL-6 Interleukin 6; hCRP = high sensitivity C-reactive protein.

Table 2. Sleep study outcomes in patients with syndromic craniosynostosis and Treacher Collins syndrome.

	No OSAS (n = 25)	OSAS (n = 23)	Mild OSAS (n = 16)	Moderate/ severe OSAS (n = 7)	No OSAS versus OSAS	No OSAS versus moderate/ severe OSAS
oAHI (range)	0.4 (0.0 – 3.9)	3.6 (1.1 – 142)	2.3 (1.1 - 8.8)	10.8 (5.4 - 142)		
ODI (range)	0.3 (0.0 – 3.2)	1.2 (0.0 – 42.6)	0.9 (0.0 - 6.5)	5.0 (0.0 - 42.6)		
Average saturation (range)	97.8 (94.6 – 99.1)	97.8 (95.7 – 98.8)	97.5 (95.7 - 98.4)	98.2 (96.8 - 98.8)		
Nadir saturation (range)	93 (78 – 98)	87.5 (70.0 - 96.0	88 (81 - 96)	87 (70 - 95)		
					P	*P*
Oxidative stress						
MDA µmol/L	6.5 (4.0 - 14.4)	6.6 (4.4 - 13.9)	6.6 (4.4 – 9.6)	8.1 (4.9 - 13.9)	0.515	0.161
Inflammatory parameters						
TNF-α pg/mL	12.3 (0.0 - 92.8)	15.1 (6.5 - 87.8)	15.1 (8.8 – 31.1)	16.6 (6.5 - 87.8)	0.440	0.533
IL-6 pg/ mL	3.4 (2.0-19.8)	3.5 (2.0-14.9)	3.6 (2.0 – 14.9)	2.9 (2.0-5.4)	0.755	0.494
hCRP mg/L	0.4 (0.0-6.0)	0.5 (0.3-5.2)	0.5 (0.3 – 3.9)	0.8 (0.3-5.2)	0.423	0.573

Data are presented as median (range). Where oAHI = Obstructive Apnea Hypopnea Index; OSAS = Obstructive Sleep Apnea Syndrome; ODI = Oxygenation Desaturation Index; MDA = Malondialdehyde in µmol/L; TNF-α = Tumor Necrosis Factor alfa in pg/mL; IL-6 = Interleukin 6 in pg/mL; hCRP = high sensitivity C-reactive protein mg/L.

The patients' BMI was normal with a median SD of 0.7 (-1.82 - 2.48) in children and a median BMI of 20.5 (15.2 – 29.4) in adults. BMI was not higher in patients with OSAS as compared to those without (children $U = 161.5$; $Z = -0.29$; $P = 0.78$) (adults $U = 10.0$; $Z = -0.11$; $P = 1.00$)

Oxidative stress did not have a correlation with the oAHI and ODI (Figures 2 and 3).

There were no statistically significant differences when comparing the OSAS group and the non-OSAS group, not even when only comparing patients with moderate to severe OSAS to those without OSAS (Table 2). MDA levels were not higher when testing OSAS patients against the reference values (median 6.6 µmol/L vs. 7.0 (4.6 - 9.4 µmol/L), $P = 0.648$).

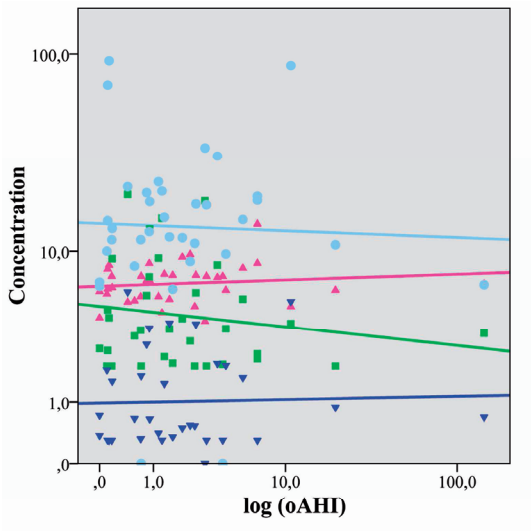

Figure 2: Correlation of MDA, TNF-α, IL-6 and hCRP with the oAHI.
Where MDA = Malondialdehyde (pink; reference 4.6 to 9.4 µmol/L); TNF-α = Tumor necrosis factor alfa (blue; reference 0.0 to 8.1 pg/mL); IL-6 = Interleukine-6 (green; reference 0.0 to 5.9 pg/mL); hCRP = high sensitivity C-reactive protein (purple; reference 0.0 to 11.0 mg/L); oAHI = Obstructive Apnea-Hypopnea-Index.
Both scales are presented as a logarithm of the original values. Correlation MDA (r=0.18, =0.24). Correlation TNF-α (r=0.069. *P*=0.69). Correlation IL-6 (r=-0.17, *P*=0.33). Correlation hCRP (r=0.063, *P*=0.72).

Inflammatory parameters did not have a corlaon with the oAHI and ODI (Figures 2 and 3). There were no statistically significant differences when comparing the OSAS group and the non-OSAS group, not even when comparing patients with moderate to severe OSAS to those without OSAS (Table 2).

IL-6 values were not higher when testing OSAS patients against the reference values (median 3.47 vs. 2.95 pg/mL (0.0 - 5.9 pg/mL), $P = 0.167$). hCRP values even were signifi-

cantly lower in OSAS patients compared to reference values (median 0.54 vs. 5.5 mg/L (0.0 - 11.0 mg/L), P < 0.001).

TNF-α was found significantly higher in both the OSAS group and non-OSAS group compared to the reference values ((median 15.1 pg/mL and 12.3 pg/mL vs. 4.05 (0.0 - 8.1 pg/mL), *P* < 0.001 and *P* < 0.001 respectively)). It was higher than reference values in 90% (26/29) of all patients with syndromic craniosynostosis and in 70% (7/10) of patients with Treacher Collins syndrome.

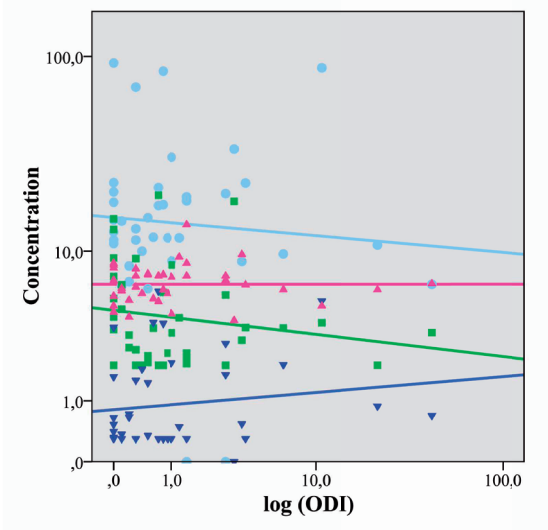

Figure 3: Correlation of MDA, TNF-α, IL-6 and hCRP with the ODI.
Where MDA = Malondialdehyde (pink; reference 4.6 to 9.4 µmol/L); TNF-α = Tumor necrosis factor alfa (blue; reference 0.0 to 8.1 pg/mL); IL-6 = Interleukine-6 (green; reference 0.0 to 5.9 pg/mL); hCRP = high sensitivity C-reactive protein (purple; reference 0.0 to 11.0 mg/L); ODI = Oxygenation Desaturation-Index. Both scales are presented as a logarithm of the original values. Correlation MDA (r=0.14 *P*=0.36). Correlation TNF-α (r=-0.070. *P*=0.67). Correlation IL-6 (r=-0.27, *P*=0.097). Correlation hCRP (r=0.079, *P*=0.63).

DISCUSSION

OSAS is highly prevalent in patients with craniofacial anomalies. It was never studied before to what extent it results in oxidative stress or systemic inflammation in these subjects with mild OSAS and without obesity.

Oxidative stress and its role in OSAS has increasingly prompted attention. To measure cellular damage, we used MDA as a marker which increases after degradation of the cellular membrane due to lipid peroxidation. Our results suggest that mild OSAS in non-obese patients does not induce daytime oxidative stress. A previous study[27] in

adults with severe OSAS (mean AHI 59 ± 5) measured increased values of thiobarbituric acid-reactive substance (TBARS), which also reflects lipid peroxidation. The level of TBARS improved after CPAP treatment.[27] Isoprostane, which is another measure for lipid peroxidation, was also found to be higher in moderate to severe OSAS (AHI >15) compared to mild OSAS (AHI 5 – 15) and no OSAS (AHI < 5) in adults.[28] However, it was also significantly higher in smoking subjects[29] and in obese subjects without OSAS as compared to lean subjects.[28] On the contrary, lipid peroxidation was tested negative in other populations with different degrees of OSAS in both obese adult patients[30] and children.[31]

Concerning inflammation, we found that IL-6 and hCRP were within the thresholds for normality; TNF-α levels were slightly increased independent of OSAS. None of the three markers for inflammation had a correlation with the severity of OSAS. Systemic inflammation as indicated by hCRP has been reported before in pediatric OSAS[32] but extensive analyses by Larkin and co-workers demonstrated that hCRP levels are only correlated with OSAS in case of AHI greater than 5.[33] Other studies however have demonstrated an increased inflammatory state in patients with OSAS. The levels of hCRP and IL-6 were increased in adult patients with OSAS.[34] It was also found that adults with OSAS (mean AHI 52.3) had an increased TNF-α level as compared to adults without OSAS (AHI 9.0).[35] Extrapolation of these data and comparison to ours is difficult since their patients without OSAS have more abnormalities in sleep studies and more extensive co-morbidity.

It was of great interest to demonstrate increases in TNF-α-levels. Since they were unrelated to the respiratory parameters, OSAS is an improbable causal factor for increased TNF-α. It is also unlikely that the increased TNF-α-levels are due to systemic inflammation, since the other inflammatory markers were not found abnormal. Moreover, the majority of our population was paediatric and lean, excluding the major burdens of comorbidity. It is of clinical relevance however that TNF-α-levels were increased since prolonged exposure to low concentrations of TNF-α levels may result in cachexia.[36] It was also previously found that TNF-α has sleep-enhancing potency, whereas for example IL-6 does not.[37-38] Physiologically, there is a circadian rhythm of TNF-α release with a nocturnal peak. In patients with OSAS, this nocturnal peak may virtually disappear and an additional daytime peak may develop.[37] Previous studies that addressed oxidative stress and inflammation as a result of OSAS mainly drew blood samples in the early morning[27-28, 30-31, 34-35] but because of altered chronobiology day-time increases in both oxidative stress determinants and hCRP have also been observed.[39-40]

Because the increased TNF-α levels were unrelated to OSAS in our population, we explored the circadian expression of the genes associated with the craniofacial anomalies in the Circa database (Circadian Expression Profiles, National Heart Lung and Blood Institute, U.S. Department of Health & Human Services). As compared to wild-type animals who have a normal function of the suprachiasmatic nucleus (or the "core clock"), it was

found that clock-mutant mice with *TWIST*, *MSX2*, *FGFR2* or *TCOF1* gene mutations reveal a cyclic pattern of end-organ metabolism with an inverted circadian rhythm. Hence, it might be possible that chronobiology is altered due to the genetic origin of the craniofacial anomalies. Dysfunction of the circadian core clock has not only been linked to OSAS, but also to mood disturbances and some psychiatric diseases.[41]

Increased TNF-α-levels have been previously linked to *TWIST* mutation (Saethre-Chotzen syndrome[1-2]) and *MSX2* mutation (Boston-type craniosynostosis[3]).[4-5] It has been proposed that TNF-α, by means of inhibition of alkaline phosphatase, alters the pathways of osteoblast and osteoclast differentiation and apoptosis[42-43] and therefore would be a cause of synostosis. On the contrary an increase in alkaline phosphatase was found in patients with Apert syndrome (as a result of a mutation in the fibroblast growth factor receptor 2 (*FGFR 2*) gene[44]; the gene that may also be affected in Crouzon or Pfeiffer syndrome[45]). To our knowledge, there has been no report on anomalies in TNF-α levels associated with Treacher Collins syndrome (*TCOF1*, *POLR1D* nor *POLR1C* genes[46-47]).

All together, possible explanations for the lack of evidence linking OSAS to oxidative stress and hCRP and IL-6 increases may reside in 1) a low overall severity of severe OSAS and 2) the absence of co-morbidities such as obesity. Increased TNF-α levels may be the result of an altered circadian rhythm, which is more likely to be present as a result of the genetic mutations rather than OSAS. It raises many additional questions for future research, including the need for laboratory studies with wild-type and mutant animal models regarding the previously mentioned genes. To conclude on the effect of OSAS on oxidative stress and inflammation, we first need to map the chronobiologic changes that come with the genetic mutations over at least 24 hours. Generally, (mild) OSAS was not associated with increased oxidative stress and systemic inflammatory day-time responses in a non-obese population with craniofacial anomalies.

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LONG-TERM RESULTS OF TREATMENT

Chapter V

Long-term assessment of facial features and functions needing more attention in treatment of Treacher Collins syndrome

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SUMMARY

Aim This study aimed to determine which facial features and functions need more attention during surgical treatment of Treacher Collins syndrome (TCS) on the long term.

Method A cross-sectional cohort study was conducted to compare 23 TCS patients with 206 controls (all ≥18 years) regarding satisfaction with their face. The adjusted Body Cathexis Scale was used to determine satisfaction with the appearance of the different facial features and functions. Wishes for further treatment of these items were questioned. For each patient an overview was made of all facial operations performed, the affected facial features and the objective severity of the facial deformities.

Results Patients were least satisfied with the appearance of the ears, facial profile and eyelids, and with the functions hearing and nasal patency ($P < 0.001$). Residual deformity of the reconstructed facial areas remained a problem in mainly the orbital area. The desire for further treatment and dissatisfaction was high in the operated patients, predominantly for eyelids reconstructions. Another significant wish was for improvement of hearing.

Conclusion In patients with TCS, functional deficits of the face are shown to be as important as the facial appearance. Particularly nasal patency and hearing are frequently impaired and require routine screening and treatment from intake onwards. Furthermore, correction of ear deformities and midface hypoplasia should be offered and performed more frequently. Residual deformity and dissatisfaction remains a problem, especially in reconstructed eyelids.

INTRODUCTION

Treacher Collins syndrome (TCS) is an inherited autosomal dominant craniofacial disorder which affects about 1 in 50,000 live births.[1] The phenotype of TCS encompasses a variety of craniofacial deformities (from mild to severe) which can affect all facial features. The typical deformities occur bilaterally and include micrognatia, anti-mongoloid slant, coloboma of the eyelids and hypoplasia of the zygomatic bones.[2] Complicated ear malformations such as meatal atresia (up to 36%) and microtia are frequently reported, as are absent, rudimentary or malformed parts of the ossicular chain,[3-4] Together, these malformations result in a conductive hearing loss, possibly present in about 50% of the patients.[5-6]

From birth onwards, TCS patients frequently undergo surgery to create a more "normal" appearance and to improve facial functions. In their early years, treatment often focuses on respiratory management of problems associated with TCS, such as obstructive sleep apnea, speech and feeding problems, and significant lagophthalmus that may threaten the cornea.[7-8] At a later stage, corrections of (peri)orbital area and orthognatic surgery are performed.[8-14] Due to the multiple affected facial features and functions, and the variable presentation, treatment is complex and management has to be made on an individual basis.

It is generally assumed that reconstructive craniofacial surgery can ameliorate satisfaction with facial appearance.[15] However, a systematic review on satisfaction studies in plastic surgery revealed that, especially studies in craniofacial surgery, were underexposed (only 8% representing 14 of all 178 studies found).[16-19] Studies on craniofacial surgery in TCS consist mainly of expert opinions, case series or retrospective cohort studies with a limited number of cases.[8, 11-12] Some present an overview (i.e. narrative reviews) on (surgical) treatment; however, because these are not systematic and are opinion based, they suffer from the same limitations as an expert opinion.[9-10, 13-14]

As a result, data on long-term outcomes of treatment in TCS are scarce. Only one descriptive study based on six patients, and another study exploring short-term follow-up in 1987, were found;[20-21] also, both those studies addressed psychosocial adjustment only. Furthermore, earlier studies had no control group and lacked a sufficient level of evidence (using patient-based outcome measures) to improve available evidence on TCS.[20, 22-23] Therefore, it remains largely unknown whether affected facial features and functions have been sufficiently treated in the long term. As assessing outcome goals for patients with a complex and variable assortment of affected facial features and functions can be difficult, the patient's own satisfaction with facial appearance and functions is considered a reliable outcome measure.[19, 24]

The present study aimed to determine which facial features and functions need more attention during treatment by: 1) assessing how satisfied TCS adults are with different

facial features and functions on the long term, also in comparison with a non-facially disfigured control group, and 2) establishing the patient's wish for further surgical treatment of certain facial features and functions at an adult age, and the objective severity of residual deformity.

PATIENTS AND METHODS

Patient selection

A cross-sectional cohort study was conducted with a TCS group and a control group. Patients in the TCS group were included if they were aged ≥18 years, diagnosed with TCS, and had been treated by the craniofacial team of the Erasmus University Medical Center in the period 1975 through 2010. A control group (also aged ≥18 years) consisted of patients without any physical disfigurement randomly selected from the waiting rooms of five general practitioner practices in Rotterdam. Exclusion criteria in both groups were: mental retardation, blindness or insufficient ability to speak/understand Dutch. The research protocol was approved by the Medical Ethical Committee of the Erasmus MC (MEC-2008-402).

Satisfaction with facial appearance and functioning

The adjusted Body Cathexis Scale (BCS; 37 items, figure 1) was used because this questionnaire contains more specific facial features than the original BCS (46 items) which comprised more features concerning the whole body.[25] Satisfaction with features of the body and their function was scored on a 5-point Likert scale (1=very dissatisfied, 2=dissatisfied, 3=neutral, 4=satisfied, 5=very satisfied). Of the 37 items, 24 dealt with physical appearance of which 14 items represented facial appearance; the remaining 13 items dealt with facial functioning. The adjusted BCS was piloted and showed good internal consistency and reliability for facial appearance, facial function, body and total BCS scores.[18]

Facial reconstructive surgery

An overview was made of all types of reconstructive procedures performed in the TCS patients. Different types of procedures were classified for different facial regions, and dichotomized into having been performed or not. A comparison was made of the frequency of dissatisfaction between operated and non-operated patients for the top five most dissatisfying facial features and functions, as rated by the patients.

Adjusted Body Cathexis Scale

This questionnaire contains questions about how satisfied you are with the following features and functions of the body. Please encircle the level of satisfaction.
Continue to encircle whether you would consider a medical treatment or not

							Would you like to change it with a medical treatment?	
1	Hair	1	2	3	4	5	yes	no
2	Smelling	1	2	3	4	5	yes	no
3	Lower extremity (legs, knees, feet)	1	2	3	4	5	yes	no
4	Sensibility nose (pain when touching)	1	2	3	4	5	yes	no
5	Height	1	2	3	4	5	yes	no
6	Cheeks	1	2	3	4	5	yes	no
7	Mouth	1	2	3	4	5	yes	no
8	Lower part trunk (hips, buttocks, genitalia)	1	2	3	4	5	yes	no
9	Smiling	1	2	3	4	5	yes	no
10	Nose	1	2	3	4	5	yes	no
11	Closure of the eyelids	1	2	3	4	5	yes	no
12	Eyebrows	1	2	3	4	5	yes	no
13	Face (in total)	1	2	3	4	5	yes	no
14	Facial profile	1	2	3	4	5	yes	no
15	Vision	1	2	3	4	5	yes	no
16	Neck	1	2	3	4	5	yes	no
17	Middle part trunk (belly, waist)	1	2	3	4	5	yes	no
18	Lacrimal function	1	2	3	4	5	yes	no
19	Facial skin	1	2	3	4	5	yes	no
20	Teeth	1	2	3	4	5	yes	no
21	Forehead	1	2	3	4	5	yes	no
22	Hearing	1	2	3	4	5	yes	no
23	Shape of head	1	2	3	4	5	yes	no
24	Ears	1	2	3	4	5	yes	no
25	Weight	1	2	3	4	5	yes	no
26	Lips	1	2	3	4	5	yes	no
27	Elevating eyebrows	1	2	3	4	5	yes	no
28	Upper part trunk (shoulders, breasts, chest)	1	2	3	4	5	yes	no
29	Eyelids	1	2	3	4	5	yes	no
30	Chewing	1	2	3	4	5	yes	no
31	Chin	1	2	3	4	5	yes	no
32	Taste	1	2	3	4	5	yes	no
33	Upper extremities (arms, wrists, hands)	1	2	3	4	5	yes	no
34	Smell of breath	1	2	3	4	5	yes	no
35	Nasal patency	1	2	3	4	5	yes	no
36	Eyes	1	2	3	4	5	yes	no
37	Speech	1	2	3	4	5	yes	no

1 = very dissatisfied
2 = dissatisfied
3 = neutral
4 = satisfied
5 = very satisfied

Figure 1. Adjusted Body Cathexis Scale

Affected facial features

Three medical doctors (SLV, RGP, RMLP), all familiar with congenital craniofacial diseases, scored independently whether facial features were affected in each patient. This was done for 14 facial features, based on standardized photographs of the patients. In addition, a validated objective scoring list for *severity* of facial deformities was scored based on standardized recent (postoperative) photographs.[26]

Desire for further treatment

For all items in the BCS, the patient was questioned regarding their wish for further treatment.

Statistical analysis

The unpaired t-test was used to analyse differences in age between the two groups. For categorical data the Fisher exact test and the Chi-squared test were used (as appropriate). Measured values are reported as mean ± 1 standard deviation (SD) or median (range) as appropriate. Multivariate analysis of covariance (MANCOVA) was conducted to compare means between the cohorts with adjustment for age, gender and educational level. The Pearson correlation coefficient was used for the correlation between satisfaction and the scored objective severity of the facial deformity. All statistical tests were two-tailed with $P \leq 0.05$ as statistically significant. Analyses were performed with Statistical Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Population and demographic characteristics

In the period 1975 through 2010, 58 patients were diagnosed with TCS. In this period four patients died (two adults). Of the 54 remaining patients, 33 were aged ≥ 18 years. Ten patients did not participate: nine due to unwillingness and one was lost to follow-up. Finally, 23 (10 males) adults (70%) participated in the present study. The control group comprised 206 adults. A significant difference in age was found between the TCS group and the control group (Table 1).

Satisfaction with facial appearance

Of the 14 facial features, 10 were scored significantly lower in the TCS group versus the control group (Table 2). In the TCS cohort, mean scores showed that the top five items providing least satisfaction were "ears", "facial profile", "eyelids" "chin" and "teeth" (Table 2); patients were satisfied with the appearance of the nose.

Table 1. Demographic characteristics of the study participants.

	TCS (n=23)		Control group (n=206)		*P*-value for differences between the groups
	%	Mean (SD)	%	Mean (SD)	
Age (years)		34.57 (13.57)		43.57 (17.08)	0.048
Gender (%)					0.657
Male	43.5%		38.3%		
Female	56.5%		61.7%		
Education level (%)					0.256
Primary school	42.8%		25.5%		
High school	33.4%		51.5%		
Post graduation	23.8%		23.0%		

* Categorical data for gender, education and marital status are displayed as frequency counts.

Table 2. Satisfaction with facial features in Treacher Collins syndrome (TCS) and wish for further treatment: outcomes of the adjusted Body Cathexis Scale

	Body Cathexis Scale (1-5) *Facial features*	Satisfaction with facial features TCS group (n=23)	Satisfaction with facial features Control group (n=206)	Differences between TCS and control group	Wish for further treatment in all TCS patients
		Mean (SD)	Mean (SD)	*P*-value	% (n)
	Face (overall)	2.87 (0.92)	3.88 (0.69)	< 0.001	39% (9/23)
1.*	Ears	2.78 (1.20)	4.00 (0.67)	< 0.001	22% (5/23)
2.	Facial profile	2.87 (0.97)	3.77 (0.80)	< 0.001	30% (7/23)
3.	Eyelids	3.00 (1.07)	3.72 (0.94)	< 0.001	35%(8/23)
4.	Chin	3.13 (1.01)	3.95 (0.62)	< 0.001	17% (4/23)
5.	Teeth	3.17 (1.03)	3.59 (0.90)	0.035	17% (4/23)
6.	Shape of head	3.26 (0.92)	3.93 (0.66)	< 0.001	9% (2/23)
7.	Cheeks	3.52 (0.95)	3.98 (0.67)	0.001	13% (3/23)
8.	Facial skin	3.57 (0.84)	3.65 (0.94)	0.468	0% (0/23)
9.	Lips	3.57 (0.73)	3.97 (0.65)	0.001	4% (1/23)
10.	Nose	3.61 (0.84)	3.82 (0.80)	0.141	13% (3/23)
11.	Neck	3.61 (0.99)	3.90 (0.73)	0.007	9% (2/23)
12.	Eyebrows	3.87 (0.69)	3.89 (0.80)	0.399	0% (4/23)
13.	Forehead	3.87 (0.55)	3.96 (0.59)	0.268	0% (0/23)

Multivariate analysis was applied with adjustment for age, gender and education level.
* Items of Body Cathexis Scale ranked ascending from least to most satisfied in Treacher Collins syndrome

Satisfaction with facial functioning

Regarding facial functioning, a significant difference was found in 9/13 items between the TCS and control group (Table 3). In the TCS group, the top five BCS items providing the most dissatisfaction were "hearing", "nasal patency", "tearing of the eyes", "smelling"

and "closure of eyelids". All these five items had a *P* value <0.001, except for "tearing of the eyes" (*P* = 0.012). (Table 3).

Table 3. Satisfaction with facial functioning and wish for further treatment in Treacher Collins syndrome (TCS): outcomes of the adjusted Body Cathexis Scale

Body Cathexis Scale (1-5) *Facial functioning*		Satisfaction with facial functioning TCS group (n=23)	Satisfaction with facial functioning Control group (n=206)	Differences between TCS and control groups	Wish for further treatment in TCS
		Mean (SD)	Mean (SD)	*P* value	% (n)
1.*	Hearing	2.68 (1.04)	3.84 (0.86)	< 0.001	35% (8/23)
2.	Nasal patency	3.00 (1.00)	3.76 (0.83)	< 0.001	26% (6/23)
3.	Lacrimal function	3.39 (0.89)	3.73 (0.90)	0.012	4% (1/23)
4.	Smelling	3.48 (0.95)	4.08 (0.75)	< 0.001	9% (2/23)
5.	Closure of eyelids	3.52 (0.67)	4.09 (0.64)	< 0.001	17% (4/23)
6.	Chewing	3.55 (0.80)	3.94 (0.75)	0.009	13% (3/23)
7.	Speech	3.55 (1.10)	4.08 (0.59)	< 0.001	13% (3/23)
8.	Smell of breath	3.57 (0.73)	3.73 (0.79)	0.200	13% (3/23)
9.	Elevating eyebrows	3.65 (0.71)	4.02 (0.60)	0.001	0% (0/23)
10.	Vision	3.65 (0.89)	3.53 (1.05)	0.935	22% (5/23)
11.	Sensibility nose	3.78 (0.95)	3.94 (0.75)	0.277	0% (0/23)
12.	Smiling	3.78 (0.85)	4.14 (0.63)	0.005	4% (1/23)
13.	Taste	4.04 (0.64)	4.16 (0.55)	0.144	0% (0/23)

Multivariate analysis was applied with adjustment for age, gender and education level.
***** Items ordered ascending from least to most satisfied in Treacher Collins syndrome

Facial reconstructive surgery

Ten reconstructive surgical procedures addressed the top five most dissatisfying facial "features" and five procedures addressed the most dissatisfying facial "functions" (Table 4). Median number of reconstructive surgeries was 3 (range 0-7), and age at "time of operation" ranged from 0-57 years. Most of the operations were performed for reconstruction of the eyelids; 11 of the 22 (50%) affected patients had one or more surgical corrections for eyelids. The two most frequently performed surgical procedures were lateral canthopexias, and autologous bone grafts in the zygomatic region. A total of 19 patients had an ear deformity, but only five patients (26%) underwent a correction of the external ear with an autologous reconstruction (three) or epithesis (two). Rhinoplasties were limited to two of 14 patients with an affected nose (14%); one had a nasal hump reduction and the other a cartilage graft for restoring tip projection with lateral osteotomies of the nasal bones. An otorhinolaryngologist was consulted in seven patients for screening/treatment of ear and hearing problems. Placement of a bone-anchored hearing aid (BAHA) was performed six times. Other otorhinolaryngological therapies

Table 4. Dissatisfaction and wish for further treatment in operated and non-operated Treacher Collins syndrome (TCS) patients for the top 5 most dissatisfying facial features and functions as addressed by reconstructive surgeries

Body Cathexis Scale	Operated TCS patients			Non-operated TCS patients		
Top 5 most dissatisfying items and facial reconstructive surgeries performed to address these items*	Patients operated (No.) %	Frequency dissatisfied patients % (No.) **	Wish for further treatment % (No.)	Frequency affected patients % (No.)	Frequency dissatisfied patients % (No.)	Wish for further treatment in affected patients % (No.)
Facial features						
No. 1 Ears						
External ear reconstruction	3/23 (13%)	33% (1/3)	0% (0/3)	80% (16/20)	30% (6/20)	31% (5/16)
Ear epithesis	2/23 (9%)	100% (2/2)	50% (1/2)	81% (17/21)	24% (5/21)	24% (4/17)
No. 2 Facial profile						
Le Fort I	4/23 (17%)	25% (1/4)	25% (1/4)	84% (16/19)	42% (8/19)	29% (5/17)
Rhinoplasty ***	2/23 (9%)	50% (1/2)	50% (1/2)	86% (18/21)	38% (8/21)	28% (5/18)
Genioplasty †	9/23 (39%)	56% (4/9)	44% (4/9)	79% (11/14)	29% (4/14)	18% (2/11)
Mandibular distraction osteogenesis †	3/23 (13%)	0% (0/3)	0% (0/3)	85% (17/20) †	45% (9/20)	35% (6/17)
No. 3 Eyelids						
Lower eyelid reconstruction ††	6/23 (26%)	50% (3/6)	67% (4/6)	94% (16/17)	18% (3/17)	25% (4/16)
Lateral canthopexia	11/23 (48%)	27% (3/11)	46% (5/11)	92% (11/12)	25% (3/12)	27% (3/11)
No. 4 Chin						
Genioplasty †	9/23 (39%)	22% (2/9)	11%(1/9)	64% (9/14)	21% (3/14)	18% (2/11)
Mandibular distraction osteogenesis †	3/23 (13%)	0% (0/3)	33% (1/3)	75% (15/20) †	25% (5/20)	13% (2/15)
No. 5 Teeth						
-	-	n/a	n/a	17% (4/23)	30% (7/23)	100% (4/4)

Table 4. Dissatisfaction and wish for further treatment in operated and non-operated Treacher Collins syndrome (TCS) patients for the top 5 most dissatisfying facial features and functions as addressed by reconstructive surgeries (continued)

Body Cathexis Scale	Operated TCS patients			Non-operated TCS patients		
Top 5 most dissatisfying items and facial reconstructive surgeries performed to address these items*	Patients operated (No.) %	Frequency dissatisfied patients % (No.) **	Wish for further treatment % (No.)	Frequency affected patients % (No.)	Frequency dissatisfied patients % (No.)	Wish for further treatment in affected patients % (No.) †††
Facial functions						
No. 1 Hearing						
BAHA	6/23 (26%)	33% (2/6)	33% (2/6)	n/a	41% (7/17)	29% (5/17)
No. 2 Nasal patency						
Septoplasty	3/23 (13%)	33% (1/3)	33% (1/3)	n/a	30% (6/20)	16% (3/20)
No. 3 Lacrimal function						
-	0/23 (0%)	n/a	n/a	n/a	17% (4/23)	4% (1/23)
No. 4 Smelling						
Septoplasty	3/23 (13%)	33% (1/3)	0% (3/3)	n/a	5% (1/20)	10% (2/20)
No. 5 Closure of the eyelids						
Lower eyelid reconstruction	6/23 (26%)	0% (0/6)	33% (2/6)	n/a	12% (2/17)	12% (2/17)
Lateral canthopexia	11/23 (48%)	18% (2/11)	36% (4/11)	n/a	0% (0/12)	0% (0/12)

n/a = not applicable

* Rank numbers identical to the results of Tables 2 and 3

** Presented are cumulative percentages of scores 1 (very dissatisfied) and 2 (dissatisfied) of the adjusted Body Cathexis Scale.

*** Rhinoplasty consisted of a hump reduction and in the other patient an auricular cartilage graft for restoring tip projection and lateral osteotomy of the nasal bones.

† Mandibular distraction osteogenesis and genioplasty addressed both the items facial profile and chin, for which satisfaction were scored separately

†† 4/6 patients received a lateral pedicled myocutaneous transposition flap of upper eyelid to the lower eyelid, one ectropion correction and one correction of a retraction

††† Whether affected or not was not scored

concerned septoplasties (three), sleep endoscopies (two), speech therapy (one), tympanoplasty (one) and tracheotomy (one). Ophthalmological consultations concerned: viral conjunctivitis, problems with closure of eyelids based on cicatricial entropion/orbicular muscle paralysis and cataract.

Affected facial features

In TCS the median number of affected facial features was 9 (4-13). Overall, the most frequently affected facial features were eyelids (96%), facial profile (87%) and ears (83%) (Figure 2).

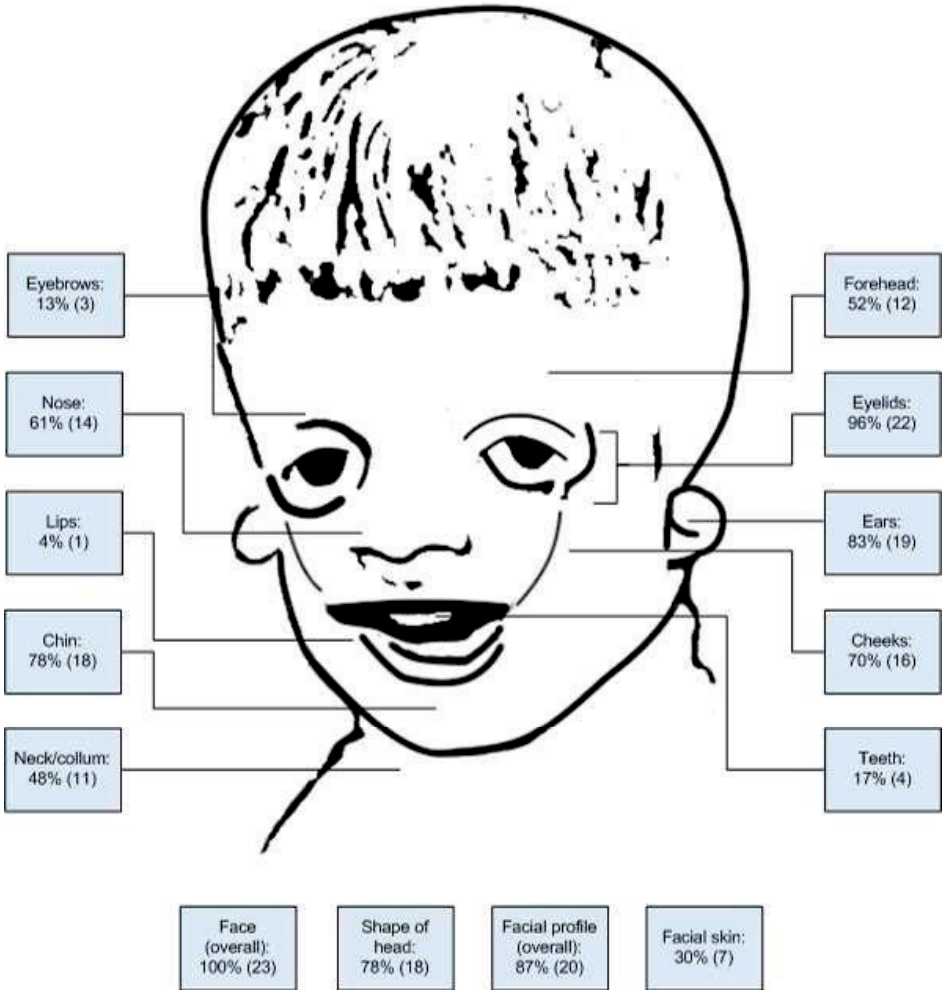

Figure 2. Facial features affected in adult patients with Treacher Collins syndrome (n=23).
Drawing of a patient with Treacher Collins syndrome. Frequency (%) and number (n) of patients affected in specific facial features are shown.

Postoperatively, the orbital zone was found to be the most "severely" affected compared to the other facial zones (Table 5). No correlation was found between a patient's satisfaction of the total face and the residual objective severity of the deformity (r =-0.186 P=0.396; Table 5).

Table 5. Objective severity of facial deformity in Treacher Collins patients on the long-term

Objective severity of facial deformity		
Zones (range scores) †	Long-term postoperative score Mean (SD)	Correlation with satisfaction with total facial appearance r (P-value)
Zone of the forehead (0-6)	0.88 (0.68)	-
Zone of the nose (0-17)	2.01 (1.06)	-
Zone of the orbits (0-31)	7.36 (2.73)	-
Zone of the maxilla (0-4)	3.12 (0.83)	-
Zone of the mouth (0-17)	0.48 (0.94)	-
Zone of the mandible (0-5)	1.51 (1.02)	-
Total score (0-80)	15.36 (5.03)	-0.186 (0.396)

† Outcomes of three independent raters

Wish for further treatment

In the "non-operated affected" patients the average wish for further treatment of the four most dissatisfying facial features (teeth excluded) was 25% (range 13-35%) (Table 4). Wish for further treatment in the "operated" patients was highest for the feature "eyelids" (5/11 after lateral canthopexia, and 4/6 after lower eyelid reconstruction). In the "non-operated" group, for "hearing" and "nasal patency" the percentage of those desiring for further treatment was 29% (5/17) and 16% (3/20), respectively.

DISCUSSION

This cohort study shows that long-term satisfaction with facial appearance is significantly lower in TCS for the ears, facial profile and eyelids compared with the control group. Satisfaction with facial functioning is also significantly lower for hearing, nasal patency, lacrimal function and smelling. In the long-term, residual deformity is a significant problem in patients who underwent reconstructive surgery to address these facial features. A large proportion of the operated patients remains dissatisfied, while the desire for correction in the remaining patients was not sufficiently addressed.

Satisfaction with facial appearance and functioning

Upper face

In overviews, treatment of the deformities of eyelids is well addressed.[8-10, 14] In the present study, TCS patients underwent repeated lateral canthopexias and/or lower eyelid reconstructions mainly with lateral pedicled myocutaneous transposition flaps of upper eyelid. Patients' dissatisfaction with the eyelids and their considerable wish for further treatment is not surprising when considering the severity of the residual deformity in the orbital zone. The soft-tissue deficiencies of the lower eyelid, hypoplasia of the zygoma, and dystopia of lateral canthi, result in a complex aesthetic and functional deficit in the orbital zone. To correct a lower eyelid, many aspects have to be taken into account, such as the position, mobility, tone, "volume" and continuity of the lower eyelid. However, also the presence of eyelashes, scars and contour deformities influence the aesthetic appearance. Unfortunately no single surgical procedure can address all these aesthetic aspects at one time and some aspects are difficult to correct. In addition, periorbital ossal deformities are difficult to correct at a young age and should preferably be treated when the face has matured.[27-28] However, soft tissue can be improved locally by lipofilling. Concerning eye-related function, patients were least satisfied with lacrimal function and closure of the eyelids. Scarring, possible congenital orbicular muscle and infraorbital rim deficiencies, together with the too low position, can result in diminished mobility and closure of the eyelids. Drainage of tears is impaired for the same reasons, but also due to possible deformities of the lacrimal system, inferiorly displaced lateral canthi, and reduced blinking function of the lower eyelid.[8, 29] However, details on lacrimal dysfunction in TCS are currently lacking. Moreover, vision loss and/or affected ocular structures are not well described; however, patients in our study were not particularly dissatisfied with this function. Interestingly, some studies report that vision loss might occur in about 37% of patients, and amblyopia and significant refractive errors in up to 33% and 17%, respectively.[30-31]

Midface

The ears were frequently affected and patients were aesthetically least satisfied with it. Relatively few surgical interventions were performed in this area. Some overviews on the treatment of TCS do not mention external ear reconstruction in detail or do not sufficiently emphasize the importance of these interventions.[8-9] Only Posnick et al. described this procedure more extensively and advocated reconstruction at age 6 years.[14, 32]

Hearing scored the lowest in "functional" satisfaction. Only six patients received a BAHA at a relatively old age (range 9-54 years). Some overviews adequately discuss hearing problems.[8, 10, 14] However, our results show that hearing rehabilitation requires more attention. A structural referral to an otorhinolaryngologist is indicated for

screening. Hearing rehabilitation must be undertaken as early as possible to initiate adequate language development in young children and to improve their integration within society. To achieve this, reconstruction of the external auditory canal or middle ear malformations in selected cases can be performed. Middle ear reconstruction may result in improved hearing, but was found insufficient to make a BAHA unnecessary.[33] In addition, a recent study on conductive hearing loss in TCS showed that BAHA implantation can be accomplished with a very low rate of complications and with significant gain in hearing (39 dB on average).[34] After gain of function, an (phased) external ear reconstruction can begin.

Our TCS patients were also dissatisfied with the feature "facial profile". Treatment of facial profile is addressed in Le Fort I, rhinoplasties and genioplasties. Patients were relatively satisfied after a mandibular advancement and Le Fort I osteotomy. Generally, more attention is paid to mandibular surgery. As a result, midface surgery is relatively underexposed in TCS; however, a Le Fort I osteotomy together with a mandibular advancement can significantly improve facial profile (and dental occlusion). Therefore, more attention should be paid to screening for maxillary hypoplasia, and a Le Fort I osteotomy should be considered more often.

Surprisingly, patients were not dissatisfied with nasal appearance and the overall wish for further treatment was only 2/14, despite the nose being frequently affected (61%). Nasal reconstruction is seldom (or not) mentioned in literature reviews.[8, 11-12] However, Posnick et al. did describe nasal reconstruction[10, 14] and suggested to perform a rhinoplasty that includes osteotomies with in-fracture, reduction of the skeletal and cartilaginous dorsal hump and removal of cephalic portions of the lower laterals and septal cartilage graft, to improve tip projection. In our opinion, nasal reconstruction should be offered if other deformities have been satisfactorily treated and after orthognatic and endonasal procedures have been performed.

Our TCS patients were significantly less satisfied with nasal patency and (probably due to the lower patency) with smelling. Endonasal surgery (septoplasty) was performed in only three patients. However, 6/20 of the "non-operated" patients were dissatisfied with nasal patency; this suggests an intrinsic nasal obstruction in patients with TCS. In addition, intrinsic nasal problems can have a causal relation with obstructive sleep apnea which is frequently present in TCS.[7, 35] Earlier overviews do not mention problems with nasal functioning.[8, 10-12, 14] This underlines the importance of a structural referral to an otorhinolaryngologist for complementary nasal investigation and treatment.[8] Primarily restoring olfactory function is difficult to achieve, but nasal patency due to obstructions can be surgically ameliorated and may improve olfactory functions by means of a better passage through septoplasty.[36-37]

Lower face

Before restoring chin protrusion, functional problems (like obstructive sleep apnea due to mandibular hypoplasia) should be excluded. Priority should be given to mandibular advancement instead of genioplasty in case of oro-/hypopharyngeal obstruction.[7] In addition, instead of genioplasty, our patients were also satisfied with the chin after a mandibular distraction osteogenesis, and wish for further treatment was low.

One study found an improvement of facial appearance as rated by the TCS patients themselves in the short term postoperatively after periorbital reconstructions and mandibular advancement.[20] However, there was no differentiation regarding specific facial features, and it remained unclear which surgical procedures were performed and whether they resulted in higher satisfaction. Our long-term results show that patients are relatively dissatisfied and no correlation exists between objective severity of the deformity and satisfaction with facial appearance.[38]

Considering our long-term results, in only ≤50% of the patients the affected facial features (i.e., ears, facial profile, eyelids and chin) were surgically corrected. More attention could be paid to corrections of ears and midface. In addition, there is often a discrepancy between satisfaction and the wish for further treatment. This might be because the patient's attention was focussed elsewhere, or because some surgical corrections were never discussed/suggested in the past. Obviously, optimising specific items in the general treatment does not warrant the success of overall treatment as this depends on long-term psychological functioning as well.[38] In the overall stigma of being facially deformed, patients have to accept their deformity and the prejudices of the society. Therefore, especially in a syndrome such as TCS, a holistic approach covering all points of attention is challenging. Acquired data could form a "physical" basis for an evidence-based protocol management in which all patients receive the same screening at certain ages. Accordingly, the variability (i.e., severity) of the phenotype determines the treatment necessary.

Limitations

Facial functions were not objectively measured, but only the patients' own experience. Due to the lack of preoperative data on satisfaction we are unable to estimate the isolated effect of surgery. Due to its rarity a relatively small sample size of the patient group was available and thus the power of the statistical analysis may be less strong. Considering the significance of the *P* values, it is unlikely that results would change dramatically with a larger patient group. However, it could still be that by using a patient group with a highly variable phenotype, significant differences are less easy to find in features that occur seldom.

CONCLUSIONS

In patients with TCS, functional deficits of the face are shown to be as important as the facial appearance. Particularly nasal patency and hearing are frequently impaired and require routine screening and treatment from intake onwards. Furthermore, correction of ear deformities and midface hypoplasia should be offered and performed more frequently. Residual deformity and dissatisfaction remains a problem, especially in reconstructed eyelids.

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Chapter VI

Long-term psychological functioning of adults with severe congenital facial disfigurement

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ABSTRACT

Background In adults with severe congenital facial disfigurement, assessment of long-term psychological impact remains limited. This study determines the long-term psychological functioning in these patients and evaluates differences compared with patients with acquired facial disfigurement and a non–facially disfigured reference group. Also explored is the extent to which psychological functioning of the congenital group is related to satisfaction with facial appearance, fear of negative appearance evaluation by others, self-esteem, and severity of the facial deformity.

Methods Fifty-nine adults with severe congenital facial disfigurement, 59 adults with a traumatically acquired facial deformity in adulthood, and 120 non–facially disfigured adults completed standardized psychological, physical, and demographic questionnaires, including the Fear of Negative Appearance Evaluation Scale, the Rosenberg Self-Esteem Scale, the Hospital Anxiety and Depression Scale, the Achenbach Adult Self-Report, the 36-Item Short-Form Health Survey, and a visual analogue scale.

Results Adults with severe congenital facial disfigurement had relatively normal psychological functioning but appeared more prone to internalizing problems than the non–facially disfigured adults. Compared with patients with an acquired facial deformity, the congenital group displayed fewer problems on the physical component score of quality of life only. Satisfaction with facial appearance, fear of negative appearance evaluation, and self-esteem were good predictors of the different aspects of psychological functioning, with the exception of the physical component score of quality of life.

Conclusions Improving satisfaction with facial appearance (by surgery), enhancing self-esteem, or lowering fear of negative appearance evaluation (by psychological support) may enhance long-term psychological functioning. Future research should focus on the individual patient and risk factors for maladjustment.

INTRODUCTION

In the literature, a lack of consensus exists concerning the issue of whether individuals with congenital facial deformities are more prone to develop psychological problems in the long term because of their deformity.[1–3] On the one hand, studies report that adults with congenital facial deformities have a higher prevalence of psychological problems, next to problems with social functioning.[4,5] These psychological problems consist of a reduced quality of life, more internalizing behavior, lower self esteem, increased depression and anxiety, and other problems.[6–9] On the other hand, several studies report no significant increase of these psychological problems in this group.[10–12] Moreover, some studies even conclude that they adjust psychosocially relatively well.[1,10,13]

Although psychological adjustment in people with disfigurement has been related to physical (visibility) and demographic characteristics,[14,15] psychologically based characteristics may be more relevant as predictors.[3] The literature points out that it is not the "objective" severity of the deformity[16,17] but rather the patient's level of satisfaction with his or her own appearance that influences psychological problems; greater dissatisfaction with appearance seems to be a predictor for higher rates of anxiety and depression and a lower rate of quality of life and self-esteem.[7,9,14] Furthermore, self-esteem itself and social anxiety are most commonly cited as being central to adjustment to physical disfigurement in general; however, results are equivocal, partly because of inconsistency in the measures and/or definitions of the constructs used.[18] People with facial disfigurement and low self-esteem are thought to be at risk for the development of psychological problems.[19]

In addition to a lack of consensus, assessment of long-term psychological functioning of adults with congenital craniofacial deformities also remains limited and studies suffer from methodologic issues.[15,20,21] Previous studies comprised mostly patients with a cleft lip– cleft palate deformity, had no control groups, used nonstandardized or nonvalidated measures, or had small sample sizes. The only available systematic review on psychosocial effects of having a cleft lip– cleft palate showed that only 15 of the 64 included studies were specifically focused on adults.[1] Only three of these studies used validated measures in combination with a nondisfigured reference group.[8,13,22] Studies on other, more severe congenital craniofacial deformities suffer from small sample sizes because of the rarity of the cases.[7]

Furthermore, comparison with other relevant groups is limited. The question of whether adults with congenital craniofacial deformities suffer less from psychological sequelae than patients with a traumatically acquired facial deformity, as suggested in the literature, has little empirical support.[23] Therefore, the present study was devised to (1) determine the impact of severe congenital facial disfigurement on long term psychological functioning; (2) evaluate whether patients with severe congenital facial

disfigurement differ from patients with acquired facial disfigurement regarding long-term psychological functioning; and (3) explore the extent to which their psychological functioning is related to satisfaction with facial appearance, severity of the facial deformity, fear of negative appearance evaluation by others (an aspect of social anxiety), and self-esteem.

PATIENTS AND METHODS

Study populations

Patients with a congenital deformity

Patients with rare facial clefts were chosen because they represent a wide spectrum of congenital facial deformities in all facial units in different sequences and with varying degrees of severity.[24,25] Medical charts of the 123 patients with an extensive rare facial cleft (Treacher Collins, oblique/ paramedian/median Tessier clefts)[24] who had surgical treatment between 1969 and 2009 at the Department of Plastic and Reconstructive Surgery of the Erasmus University Medical Center were reviewed. A total of 48 patients were excluded because they were dead (*n* =4), had incomplete data (*n*=9), were younger than 18 years (*n*=32), were mentally retarded (*n* =1), were blind (*n* =1), or had insufficient knowledge of the Dutch language (*n*=1). The remaining 75 patients were invited to participate.

Patients with an acquired facial deformity

This group consisted of patients who suffered from facial trauma at an adult age and had an operation between 1991 and 2007. Only patients with a minimum follow-up of two years after initial reconstruction were selected, because it was more likely that physical and/or psychological consequences of the trauma had stabilized. Medical charts of these patients were reviewed, and all patients with other visible congenital or traumatic disfigurements, or who had suffered from personal assault, were excluded. Of the remaining 140 patients, another 36 patients were excluded because they were dead (*n* = 2), had incomplete data (*n* =4), were younger than 18 years (*n* =21), or had insufficient knowledge of the Dutch language (*n* =9). As a result, 104 met the inclusion criteria.

Reference group without facial disfigurement

This reference group was composed of the patient population from five randomly selected general practitioner practices in Rotterdam and of Erasmus Medical Center staff without any congenital or acquired visible deformity. They were recruited by means of

posters, and exclusion was based on criteria similar to those applied in the congenital group.

Design and procedure

A clinical-empirical cross-sectional design was used. Ethical approval was obtained from the local medical ethical committee (MEC-2006-121). A patient information form, questionnaires, an informed consent form, and a stamped return envelope were sent by mail to the home addresses of the patients; current addresses were checked with the municipal population registry. Within one month, patients had to decide on participation. Patients could withdraw at any time. Patients who did not return their questionnaires within one month were contacted again by mail. If a patient declined to participate, his or her reason was requested by means of a telephone conversation. The reference group completed the same questionnaires at home and returned them by mail.

Assessments

Demographic information

This provided data on age, sex, and educational level.

Fear of negative appearance evaluation

The six-item Fear of Negative Appearance Evaluation Scale is a self-report assessment tool measuring apprehension about appearance evaluation on a five-point Likert scale. The Fear of Negative Appearance Evaluation Scale has good internal consistency and a convergent validity similar to measures of body image in the field of eating disorders.[26]

Self-esteem

The Rosenberg Self-Esteem Scale is a 10-item self-report inventory measuring self-esteem on a four-point Likert scale.[27] Good reliability and validity have been demonstrated.[28]

Severity of facial disfigurement

Objective severity of facial disfigurement was scored independently by two experts in each patient of both patient groups based on recent standardized photographs and using the scoring list of Versnel et al., with an objective scoring approach for facial disfigurement.[29]

Anxiety and depression

The Hospital Anxiety and Depression Scale is a 14-item self-report measure based on a four-point Likert scale. It comprises two internal scales (i.e., Anxiety and Depression) and

has been found a robust and effective screening tool.[30] A score of 11 and above indicates clinically significant levels of anxiety and depression.[31]

Adaptive functioning/behavioral problems

The Adult Self-Report assesses people's perception of their own functioning (age range, 18 to 59 years). It consists of 126 items on problem behaviors, using a three-point Likert scale, which are categorized into subscales.[32] The two broad band scales (i.e., Internalizing and Externalizing) and the Total Problem Score were used. Cutoff scores for the clinical range per age group and sex for these three total scores are available. Good reliability and validity have been demonstrated for the American version, and it has been used in Dutch population samples.[32,33]

Quality of life

The 36-Item Short-Form Health Survey is a 36-item measure of quality of life, including physical and mental health. The physical domain subscales are physical functioning, role problems, bodily pain, and general health. The mental domain subscales are vitality, social functioning, problems with work and daily activities attributable to emotional problems, and general mental health. The Physical and Mental Component Summary measures were used; they take the correlation among the eight 36-Item Short-Form Health Survey subscales into account and are calculated with U.S. norm scores from 1998 as a reference point.[34] With this norm-based scoring (mean (SD)) (50 (10)), an individual respondent's score on Physical Component Summary and Mental Component Summary below 45 implies a health status below the average range. Because these international norm scores were available, the reference group did not complete the 36-Item Short-Form Health Survey to reduce the number of questionnaires. The 36-Item Short-Form Health Survey has good psychometric properties.[35]

Satisfaction with facial appearance

A visual analogue scale was used as a 100-mm continuous horizontal line anchored at the poles, with "very dissatisfied" at the left and "very satisfied" at the right pole, to measure the degree of satisfaction with the patient's current facial appearance. The visual analogue scale has shown reliability and validity in studies on facial appearance.[8,10] Measures for body image[36] (e.g., the Multidimensional Body-Self Relations Questionnaire) have not yet shown significant differences in studies on facially disfigured persons, not even when using the facial subscale.[37] Therefore, the visual analogue scale was preferred.

Statistical analysis

The mean and SD were used for metric variables, and percentages were given for categorical variables. Fisher's exact test was used to analyze differences in categori-

cal variables between independent groups. Comparison of means between the three groups was performed with analyses of covariance with adjustments for age, sex, and education level. The percentage of patients within the clinical range in each group was calculated with the raw scores according to the above-mentioned cutoff points for the Hospital Anxiety and Depression Scale and the Adult Self-Report. Differences in these percentages between groups were analyzed with a logistic regression analysis with two groups as outcome variable, and adjustments for age, sex, and education level (Hospital Anxiety and Depression Scale) or only education level (Adult Self-Report; because cutoff scores take age and sex into account). Comparison of the means of the Physical Component Summary and Mental Component Summary between the congenital group and the U.S. norm scores was performed with an unpaired *t* test. The predictive value of satisfaction with facial appearance, fear of negative appearance evaluation, self-esteem, and objective severity of facial disfigurement for the different aspects of psychological functioning were analyzed using the method of multiple linear regression analysis (procedure Enter) to identify the importance of the predictors jointly. Statistical analysis was conducted with version 17.0 of the computer program SPSS (SPSS, Inc., Chicago, Ill.).

RESULTS

Of the 75 rare facial cleft patients, 59 (79 percent) agreed to participate. The remaining 16 patients refused: eight did not respond to the letters (four lived abroad), three had traumatic experiences with treatment, two refused because they had already talked about it to the media in the past, and three patients found it psychologically too difficult.

Of the 104 patients with a traumatically acquired facial disfigurement, 59 (57 percent) participated. The average time from injury to the assessments was seven years (range, 2 to 16 years). The majority of the remaining patients in this group did not respond to the letters and could not be contacted; however, they did not differ from the sample studied on any demographic or surgical variables.

Demographic characteristics

Because the congenital deformity group showed significant differences compared with the acquired deformity patients on sex and age, and compared with the reference group on education level, all analyses were adjusted for sex, age, and education level (Table 1).

Differences between groups

There were no significant differences between the congenital and reference groups in the mean scores of anxiety and depression; Internalizing, Externalizing, and Total Behavioral Problem scores; and the Physical and Mental Component Summary measures of

Table 1. Demographic characteristics of the study groups

	Groups			Differences between groups (*p*)*	
	Congenital (*n* = 59)	Acquired (*n* = 59)	Reference (*n* = 120)	Congenital vs. acquired	Congenital vs. reference
Sex %				0.01	0.73
Male	32.2	41.4	29.4		
Age, yr				0.01	0.21
Mean	34.1	43.1	36.7		
SD	12.9	14.6	16.4		
Minimum/ maximum	18/74	18/84	18/79		
Education level %				0.68	0.04
Primary school **	35.1	27.6	17.2		
High school**	47.4	55.2	59.5		
Postgraduation**	17.5	17.2	23.3		
Severity of facial deformity				0.001	-
Mean score	13.9	6.44	-		
SD	7.65	5.0	-		

*Corrected for multiple testing, α = 0.025 (two-tailed).
** Represent column percentages.

quality of life (Table 2). Mean scores of anxiety and depression fell within the "normal/ nonclinical" range in all three groups. The percentage of patients with a clinical level of anxiety was 11 percent in the congenital group, 11 percent in the acquired group, and 3 percent in the reference group. After adjustments, the difference between the congenital group and the reference group was nonsignificant (p=0.29). Six percent in the congenital group, 9 percent in the acquired group, and 4 percent in the reference group demonstrated a clinical level of depression. Again, after adjustments, no significant difference was found between the congenital and reference groups (P = 0.66).

Externalizing and Total Problem Scores showed no significant difference on the percentage of patients within the clinical range between the congenital and reference groups. The values for Externalizing were as follows: congenital group, 10 percent; acquired group, 7 percent; reference group, 5 percent (p=0.56). The values for Total Problem Scores were as follows: congenital group, 11 percent; acquired group, 9 percent; reference group, 6 percent (P = 0.31). However, the congenital group had more patients within the clinical range on Internalizing problem scores (25 percent) than the reference group (13 percent), although the difference was not significant (P =0.08). In the acquired group, 21 percent of the patients had internalizing problems.

The only significant difference between the congenital and the acquired group was on the Physical Component Summary. The mean score of the acquired group was lower than the U.S. norm population, whereas the congenital group scored better. In the con-

Table 2. Differences between groups on psychological aspects

	Mean† (SD) Group scores			Differences in group scores (*p*)*	
Psychological aspects	Congenital (*n* = 59)	Acquired (*n* = 59)	Reference (*n* = 120)	Congenital vs. acquired	Congenital vs. reference
Anxiety	4.3 (3.9)	5.0 (4.0)	3.8 (3.9)	0.40	0.54
Depression	4.1 (3.7)	5.4 (3.6)	4.4 (3.6)	0.08	0.76
Internalizing	15.3 (10.8)	14.3 (10.9)	12.2 (10.7)	0.99	0.10
Externalizing	9.3 (6.3)	8.5 (6.4)	7.2 (6.3)	0.86	0.08
Total problem**	43.1 (24.5)	39.5 (24.7)	34.3 (24.4)	0.86	0.06
PCS	52.0 (8.4)	47.8 (8.4)	-	0.02	0.13***
MCS	51.6 (10.2)	50.6 (10.3)	-	0.68	0.23***

† Adjusted for mean values of age, sex and education level.
*Corrected for multiple testing, α = 0.025 (two-tailed).
** Total problem score (Adult Self-Report).
*** Calculated with 1998 U.S. norm scores as the reference group. For PCS, mean (SD) = 50 (10), *n* = 6742; for MCS, mean (SD) = 50 (10), *n* = 6742

genital group, 13 percent scored lower than 45 on the Physical Component Summary and 31 percent had a Mental Component Summary score lower than 45, implying a health status below the average range. The percentages of patients within the clinical range showed no significant difference between the congenital and acquired groups regarding anxiety (p=0.70), depression (P = 0.70), internalizing (P =0.73), externalizing (P = 0.66), or total behavioral problems (P =0.66).

Predictors of the psychological aspects

Apart from objective severity of the facial disfigurement, they all appear to be significant predictors (p value) for the different aspects of psychological functioning, except for the Physical Component Summary (Table 3). Self-esteem is the strongest predictor (β) for all aspects of psychological functioning; the higher the self-esteem, the better the psychological functioning. Satisfaction with facial appearance is not a significant predictor for externalizing problems.

The scores of the congenital deformity group on fear of negative appearance evaluation (18.02 ± 6.38) and satisfaction with facial appearance (4.26 ±2.19) were not significantly different from those of the acquired deformity group (fear of negative appearance evaluation, P = 0.19; satisfaction with facial appearance, P =0.54) but differed significantly from those of the reference group (fear of negative appearance evaluation, P =0.001; satisfaction with facial appearance, P = 0.001). The scores of the congenital group on self-esteem (31.81±5.16) did not differ significantly from those of the acquired group (P = 0.64) or the reference group (P = 0.07).

Table 3. Predictors of psychological aspects

	Candidate predictors							
	p				*β*			
Psychological aspects	SFA	FNAE	SE	OS	SFA	FNAE	SE	OS
Anxiety	0.01	0.01	0.001	0.64	-0.45	0.35	-0.64	-0.08
Depression	0.001	0.001	0.001	0.94	-0.53	0.50	-0.71	-0.01
Internalizing	0.02	0.01	0.001	0.05	-0.40	0.42	-0.61	0.12
Externalizing	0.06	0.02	0.01	0.69	-0.31	0.36	-0.51	-0.07
Total problem	0.02	0.01	0.001	0.82	-0.38	0.38	-0.57	0.04
PCS	0.17	0.44	0.17	0.48	0.18	-0.10	0.19	-0.09
MCS	0.01	0.01	0.001	0.62	0.48	-0.42	0.71	0.18

β, standardized regression coefficient; SFA, satisfaction with facial appearance; FNAE, fear of negative appearance evaluation; SE, self-esteem; OS, objective severity of the facial disfigurement; PCS, Physical Component Summary; MCS, Mental Component Summary.

DISCUSSION

This study demonstrates that adults with severe congenital facial disfigurement appear to have rather "normal" psychological functioning. No differences were found on mean scores of anxiety, depression, behavioral problems, or quality of life between the three groups, with the exception of the Physical Component Summary. Despite the normal group scores, it is important not to overgeneralize to the individual.[3] This is supported by the fact that a subset of patients of the congenital group scored within the clinical range on the different psychological aspects: 11 percent had anxiety, 6 percent had depression, 10 percent had externalizing problems, and 25 percent had internalizing problems. Therefore, although the latter was not significant, adults with congenital facial deformities seem prone to internalizing problems. Regarding quality of life, the Mental Component Summary was below the average range in 31 percent of the patients in the congenital group, and the Physical Component Summary was below the average range in 13 percent of the patients. This implies that despite a normal quality of life in the congenital group, attention should be paid to the presence of mental distress in each individual.

Several studies support positive psychological adjustment in patients with congenital craniofacial deformities.[1,38] In most studies, little attention is paid to normal results, and it seems difficult to accept that people manage to live a relatively normal life with a severe disfigurement.[39,40] How do we interpret the rather normal psychological functioning found in the present study?

First, change in internal standards, values, and meaning of quality of life can cause an adaptation process, resulting in a good self-perceived quality of life and psychological

functioning. Mechanisms to achieve this are coping, social comparisons, and adjustment of goals and expectations.[41]

Second, facial deformity is one of many naturally occurring stressors in life that must be adapted to.[39] People without a facial deformity also have to deal with all types of occurring/immanent stressors that can have an impact on psychological functioning comparable to a facial deformity.

Third, methodologic issues could explain the lack of differences in psychological functioning. Disease- specific questionnaires reveal more differences than generic questionnaires; therefore, more questions related to facial appearance should be used. In addition, as demonstrated above, an individual approach seems important and should not be conducted by psychometric tests only.[42]

Looking at the differences between the congenital deformity and acquired deformity populations, the acquired deformity group suffered significantly more from physical problems (Physical Component Summary) than the congenital deformity group. This implies that adaptation to physical problems might take a long time, or that traumatically acquired facial disfigurement could be related to more physical impairment. Furthermore, because congenital deformities occur before memory, a patient has no knowledge of how life would be without the disfigurement and concomitant physical problems.[43]

The scores on the Mental Component Summary imply that both groups have no psychological distress. Thus, the fact that people with a congenital facial deformity have had more time to get used to their deformity does not result in better long-term psychological functioning.

Previous studies on facial trauma patients report more anxiety, depression, and psychological stress compared with the normal population.[44,45] However, in contrast to the present study, these latter studies were conducted in acute settings and assessed patients with concomitant injury and assault; this might explain the better outcome in the present study.

Concerning the evaluation of predictive factors, self-esteem appears the strongest predictor for all aspects of psychological functioning. Therefore, when low, self-esteem should be assessed and ameliorated by psychological support.

Objective severity has no predictive value for psychological distress, but self-perceived satisfaction with facial appearance does. Therefore, during treatment, patients' realistic wishes and expectations regarding their facial appearance should be taken into account. Fear of negative appearance evaluation appeared to be a good predictor of psychological functioning. Therefore, psychological support should also be focused on training patients to rely less on the opinions of others. Physical problems are not influenced by the examined predictors.

One of the limitations of the present study is the possible selection bias, although the participation rate in the congenital deformity group (79 percent) and the traumatically acquired deformity group (57 percent) can be considered relatively high compared with other studies[21,38]; nevertheless, outcomes in both of these groups may be worse than presented here. Also, the reference group consisted of a mixture of people, which might bias the outcomes. To enable better comparison, the significant baseline characteristics among the three groups were statistically adjusted in all analyses. Furthermore, not all aspects of psychological functioning and predicting factors were evaluated. The fact that the reference group did not complete the 36-Item Short-Form Health Survey is an additional limitation of this study.

CONCLUSIONS

Adults with congenital facial disfigurement have rather normal psychological functioning but are more prone to internalizing problems. They differ from patients with an acquired facial deformity only on physical problems. Improving the patient's satisfaction with his or her facial appearance by surgery, and improving self-esteem or lowering fear of negative appearance evaluation by psychological treatment, may enhance long-term psychological functioning over the long term. Therefore, future research should focus on the individual patient and risk factors for maladjustment rather than on group comparisons, also because of the inconsistency of the results published.

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THE NOSE: ENDONASAL AND EXTERNAL NASAL DEFORMITY AND SATISFACTION WITH FUNCTION AND APPEARANCE

Chapter VII

Nasal sequelae of Treacher Collins syndrome

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ABSTRACT

Objective This study aimed to determine external and endonasal deformity, and satisfaction with nasal functioning and appearance, in Treacher Collins syndrome.

Study design Cross-sectional cohort study.

Methods Eleven adult Treacher Collins patients were compared with 151 controls regarding satisfaction with nasal functioning and appearance by means of the Nasal Appearance and Function Evaluation Questionnaire. In all patients with Treacher Collins external nasal deformities were scored on standardized digital photographs of the nose as rated independently by three experienced physicians. Endonasal deformity was determined by standardized nasal endoscopy.

Results Patients were relatively satisfied with the various esthetic nasal subunits. The most significant functional problems were snoring (P=0.001) and quality of phonation (P=0.003). The main external nasal deformities were the dorsal hump (73%), external deviation (≤ 55%), the bifid or bulbous nasal tip (55%), and columellar septal luxation (55%). In 82% of the patients a septal deviation was found, often associated with spurs.

Conclusion Satisfaction with esthetics of the nose was fair, but these patients suffer from the functional problems of snoring and impaired quality of phonation. A structured nasal ENT physical examination with nasal endoscopy might determine aspects requiring more attention during treatment. Septorhinoplasty can be performed at an adult age if there is a considerable esthetic wish of the patient and/or nasal obstruction combined with septal deviation. Attention should be paid to dorsal hump reduction, correction of deviated external osseous framework, septoplasty, and correction of the nasal tip shape.

INTRODUCTION

Treacher Collins syndrome is a rare congenital craniofacial syndrome with an incidence of 1 in 50,000 live births and an autosomal dominant inheritance pattern.[1-3] In this syndrome, craniofacial deformities consist of bilateral defects in the periorbital region, mandibular hypoplasia and hypoplasia of zygoma and microtia, and middle-ear deformities.[4] Treacher Collins syndrome is mainly caused by mutations in *TCOF1* which compromise the ability of neuroepithelial cells to proliferate during early embryogenesis, leading to neuro-epithelial apoptosis (programmed cell death) and, finally, affecting development of the first and second pharyngeal arch. Haploinsufficiency of *TCOF1* causes hypoplasia of the frontonasal and maxillary regions, cleft palate, and mandibular hypoplasia.[5-6] Other causative mutations for Treacher Collins syndrome can be found in *POLR1D* and *PORLR1C*.[3]

Although the nose can be severely affected, as illustrated by a case report of arhinia,[7] the nose is not always mentioned as a craniofacial feature in Treacher Collins syndrome.[8] Only one study in 1989 performed morphometry of the external nose in Treacher Collins (mainly in children), and only one group has reported a possible surgical treatment for the deformities as described by Farkas and Posnick in 1989.[9-11] In addition, current treatment overviews seldom (or never) describe nasal reconstruction or other methods of treatment of the nose.[12-15] Moreover, these few specific overviews/studies describe only the external nose and do not include nasal functioning. However, nasal functioning warrants attention because intrinsic nasal problems can have a causal relation with obstructive sleep apnea, which is frequently present in Treacher Collins syndrome.[16-18] Although other upper airway deformities have (to some extent) been described in Treacher Collins syndrome *endonasal* deformities have not - even though this is essential to at least exclude them as a focus of obstructive sleep apnea.[19-20] In general, there is a lack of literature and data on nasal deformity and nasal functioning in Treacher Collins syndrome.

Therefore, in adult patients with Treacher Collins syndrome, the present study aimed to determine: 1) patients' problems with nasal functioning, and their satisfaction with nasal appearance, using a validated questionnaire compared with controls; physicians' assessment of: 2) external nasal deformities using standardized digital photographs, and 3) endonasal deformities by means of flexible endoscopy.

PATIENTS AND METHODS

Patient selection

We conducted a single-center cross-sectional cohort study. Patients in the Treacher Collins group were included if they had been diagnosed with Treacher Collins by the multidisciplinary craniofacial team of the Erasmus University Medical Center since 1974 (i.e. during a 37-year period). All adult patients (age ≥ 18 years) were eligible for inclusion. All investigations (described below) took place at our outpatient clinic on the same day (per patient) in October 2012.

In addition, data on a control group of 151 adults were obtained from the Nasal Appearance and Function Evaluation Questionnaire (see below). Exclusion criteria for both groups were age < 18 years and, in the control group, any visible facial deformity.

The study was approved by the Medical Ethics Committee of the Erasmus MC (MEC-2011-135).

Reconstructive surgeries, obstructive sleep apnea, medication and allergies

In the Treacher Collins group, an inventory was made of known allergies and currently used medication. An overview was made of all facial reconstructive surgeries performed, including endonasal surgeries. The presence of obstructive sleep apnea, as determined by polysomnography, was known for all patients.

Satisfaction with nasal functioning and appearance

The Nasal Appearance and Function Evaluation Questionnaire was filled out by both the Treacher Collins and the control group. This questionnaire has been validated for patients with a nasal reconstruction and consists of 14 questions answered on a five-point Likert scale.[21] The Nasal Appearance and Function Evaluation Questionnaire consists of two parts; the first consists of sevenquestions on nasal function, including airway passage, snoring, olfaction, dry mucosa, epistaxis and phonation; answers can be scored ranging from "always" to "never". The second part consists of seven questions addressing satisfaction rated per different subunit of the nose, and overall satisfaction (Figure 1); answers can be scored ranging from "very dissatisfied" to "very satisfied".

External nasal deformity

External nasal deformities were scored in the Treacher Collins group on standardized digital photographs of the nose taken by a professional medical photographer of the Erasmus MC. Three medical specialists, i.e. two craniofacial surgeons and one otorhinolaryngologist (IMJM, JJNMM and RMLP; all three involved in operating congenital craniofacial malformations), evaluated the photographs independently using a detailed and structured external nasal deformity scoring assessment (Figure 2). A total of 29 items

Items of the Nasal Appearance and Function Evaluation Questionnaire

		always	*mostly*	*every now and then*	*hardly ever*	*never*
1.	How often do you have trouble breathing through your nose?	1	2	3	4	5
2.	How often do you snore?	1	2	3	4	5
3.	How often can you smell odors?	1	2	3	4	5
4.	How often do you have trouble with nasal crusts?	1	2	3	4	5
5.	How often do you have a bloody nose?	1	2	3	4	5
		very poor	*poor*	*moderately*	*good*	*excellent*
6.	How do you assess your quality of speech?	1	2	3	4	5
		very dissatisfied	*dissatisfied*	*moderately*	*satisfied*	*very satisfied*
7.	How satisfied are you with your total nasal functioning?	1	2	3	4	5
8.	How satisfied are you with your nasal tip appearance?	1	2	3	4	5
9.	How satisfied are you with your nasal wing(s) appearance?	1	2	3	4	5
10.	How satisfied are you with your nasal dorsum appearance?	1	2	3	4	5
11.	How satisfied are you with the size of your nostril(s)?	1	2	3	4	5
12.	How satisfied are you with the color of your nasal skin?	1	2	3	4	5
13.	How satisfied are you with your nasal position?	1	2	3	4	5
14.	How satisfied are you with your total nasal appearance?	1	2	3	4	5

Figure 1. Nasal Appearance and Function Evaluation Questionnaire

were scored using standard terminology.[22] Nasal deformities were scored by all raters at the same angle, in frontal, caudal and/or lateral view on six standardized photographs of the nose (available per patient). After filling out the assessment a consensus was reached when at least two-thirds of raters scored the specific deformity.

Endonasal deformity

In the Treacher Collins group, an experienced otorhinolaryngologist (RMLP) performed anterior rhinoscopy and standardized nasal endoscopy (using a flexible laryngoscope) to determine endonasal deformities. In relation to the nasal septum, deviations, spines

External nasal deformity assessment form

Patient identification number:

Nose: assess in frontal view only:					
Upper 1/3 of the nose					
Deviation	None	Left	Right		
	No in/outfraction	Infraction left	Outfraction left	Infraction right	Outfraction right
Width	Normal	Tight	Broad		
Middle 1/3 of the nose					
Deviation	None	Left	Right		
Shape	Normal	Inverted V			
Lower 1/3 of the nose					
Nasal tip					
Deviation	None	Left	Right		
Shape	Normal	Bulbous	Bifid	Prominent	
Basis					
Width	Normal	Tight	Broad		
Alar flaring left	None	Present			
Alar flaring right	None	Present			
Nose: assess in caudal view only:					
Basis					
Width	Normal	Tight	Broad		
Nares left	Normal (oval)	Slit-shaped	Round		
Nares right	Normal (oval)	Slit-shaped	Round		
Columella					
Septal luxation	None	Left	Right		
Width	Normal	Tight	Broad		
Length	Normal	Short	Long		
Nose: assess in lateral view only:					
Nasofrontal angle	Normal	Deep	Flat		
Length	Normal	Short	Long		
Height					
Hump	None	Present (n.f.s.)			
Saddle	None	Present (n.f.s.)			
Nasal tip					
Projection	Normal	Under projection	Over projection		
Rotation	Normal	Under rotated	Over rotated		
Columella	Normal	Retracted	Columellar show		
Alar region (left)	Normal	High	Low		
Alar region (right)	Normal	High	Low		
Nasolabial fold (left)$	Normal (sharp)	Blunt			
Nasolabial fold (right)$	Normal (sharp)	Blunt			
Other	Double break present (normal)	Double break not present			

Figure 2. Standardized external nasal deformity assessment

N.f.s. : Not further specified

$ Assess in both lateral and frontal view

and spurs were described. Deformities of the turbinates, aspect of the choanae and nasal floor, and signs of rhinitis were noted.

Statistical analysis

Analyses were performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, USA). All statistical tests were two-tailed with $P < 0.05$ designated as statistically significant. For categorical data the Chi-squared test was used and for continuous data the Wilcoxon signed rank test was used in case of non-normally distributed data. For all outcome variables of the Nasal Appearance and Function Evaluation Questionnaire, three candidate covariates ("gender", "age" and "clustered education level") were tested separately. Education level was found to be a confounder of importance. Multivariate linear regression (with bootstrapping in case of non-normally distributed data) was conducted to compare means between the Treacher Collins and control group for separate items of the Nasal Appearance and Function Evaluation Questionnaire by adjusting for clustered education level. Measured values are reported as mean ± 1 standard deviation or median (range/interquartile range), as appropriate.

RESULTS

Demographic characteristics

In the period 1974 to 2010, 57 patients were diagnosed with Treacher Collins syndrome and, during this period, four patients died. In 2012 (when this research started), of the 53 available patients 40 were aged ≥ 18 years, and two lacked a current address. Of the

Table 1. Demographic characteristics of the study participants.

	Treacher Collins group (n=11)	Control group (n=151) †	*P*-value for differences between patients and controls
	Median (range)	Median (range)	
Age (years)	41 (20-61)	40 (19-93)	0.931
Gender			
Male	27.3%	40.4%	0.390
Female	72.7%	59.6%	
Education level			
Primary school & 10th grade	27.3%	14.6%	0.156
High school & Community college	27.3%	57.0%	
Postgraduation	45.5%	28.5%	

Categorical data for gender and education are displayed as frequency counts.
† The control group was used to compare outcomes from the Nasal Appearance and Functional Evaluation Questionnaire.

remaining 38 adult patients who were approached by letter, 11 participated (29%) and 27 were unwilling to participate; this patient group included three males (27%) and all were (pale-skinned) Caucasian. There were no significant differences in age, gender and clustered education level between the patients and controls (Table 1).

Reconstructive surgeries, obstructive sleep apnea, medication and allergies

Of the 11 included patients, five had previously undergone nasal surgery of which two external rhinoplasties and four endonasal procedures (Table 2). Three of the 11 patients suffered from obstructive sleep apnea (two mild; one severe who used *continuous positive airway pressure*). Two of these patients suffered from dust mite allergy (both from hay fever, and one had contact allergy for adhesive plasters and nickel). One of these latter patients used (long-term) oral antihistamine, and two used nasal steroid sprays

Table 2. Previous nasal surgery, obstructive sleep apnea and endonasal deformities found in 11 adult patients with Treacher Collins syndrome

			Anatomic site of deformity				
		Severity of obstructive sleep apnea	Turbinates	Nasal septum		Nasal floor	Choana
Cases	Previous nasal surgery			*Deviated*	*Other*		
No. 1	-	-	Bullous middle turbinate	Convex	Spur	-	-
No. 2	-	-	-	-	Broad divergent perpendicular plate	-	-
No. 3	- Surgically assisted rapid maxillary expansion - Le Fort I osteotomy - Dacryocystorhinostomy	Mild	-	Dorsal	Spur Septal spine	-	-
No. 4	- Trauma†† - Choanal reconstruction - Le Fort I osteotomy	-	Inferior turbinates reduced †	Dorsal vomer	Septal spina	Higher	-
No. 5	- Septoplasty - Turbinectomy	-	-	-	Spur	-	-
No. 6	-	-	-	Dorsal	Spur	-	-
No. 7	- Nasal hump reduction	Severe	-	Dorsal	Spur	-	-
No. 8	- Restoring tip projection with cartilage graft and lateral osteotomy of the nasal bones.	-	-	Dorsal	-	-	-
No. 9	-	-	-	Dorsal	Spur	-	-
No. 10	-	-	-	Caudal	Septal spine	-	-
No. 11	-	Mild	-	Dorsal	Spur	-	-

† After bilateral surgical inferior turbinate reduction

†† No nasal surgery performed related to this trauma.

incidentally during spring time. Another patient used sodium chloride nasal flushes and a nasal steroid spray; she also used continuous positive airway pressure for her obstructive sleep apnea and was *not* known to have an allergy.

Satisfaction with nasal functioning and appearance

All patients filled out the Nasal Appearance and Function Evaluation Questionnaire. The following complaint/function was scored most frequently: "snoring" median two (i.e. "mostly"), (interquartile range 1-3) (Table 3). All patients snored, of whom 46% (5/11) "every now and then" and the remainder "mostly" (18%, 2/11) or "always" (36%, 4/11); this item showed a significant difference between patients and controls (*P*=0.001). The quality of phonation was scored "moderately" in 27% (3/11) of patients and showed a significant difference compared with controls (*P*=0.003). Of the 11 patients, five (45%) scored "trouble breathing through the nose" as "every now and then" or more frequently (i.e. "mostly" or "always"); this score was not significantly different compared with controls. For all items regarding satisfaction with nasal appearance ≥ 81% (9/11) scored "satisfied" or "very satisfied" with a similar interquartile range (4-4).

Table 3. Satisfaction with nasal functioning and appearance in Treacher Collins syndrome: outcomes of the Nasal Appearance and Function Evaluation Questionnaire

	Treacher Collins group (n=11)	Control group (n=151)	Differences between groups
	Median (interquartile range)	Median (interquartile range)	*P*-value
1. Trouble breathing through nose	4 (3-4)	4 (3-4)	0.506
2. Snoring	2 (1-3)	4 (3-5)	0.001
3. Olfaction	2 (1-3)	2 (1-2)	0.202
4. Dry mucosa	4 (3-5)	4 (3-5)	0.361
5. Epistaxis	5 (4-5)	5 (4-5)	0.298
6. Quality phonation †	4 (3-4)	4 (4-5)	0.003
Satisfaction with			
7. Overall function	4 (4-4)	5 (4-5)	0.184
8. Nasal tip	4 (4-4)	5 (4-5)	0.391
9. Ala nasi	4 (4-4)	5 (4-5)	0.083
10. Nasal dorsum	4 (4-4)	5 (4-5)	0.067
11. Nostril size	4 (4-4)	5 (4-5)	0.031
12. Color	4 (4-4)	5 (4-5)	0.005
13. Nasal position	4 (4-4)	5 (4-5)	0.014
14. Total nasal appearance	4 (4-4)	5 (4-5)	0.025

Multivariate analysis was applied with adjustment for clustered education level.
† Regarding this item one value was missing

Table 4. External nasal deformity in Treacher Collins syndrome: outcomes of consensus of three independent raters

Nasal item								Consensus %*
Upper 1/3 of the nose								
Deviation	None	45% (5/11)	Left	18% (2/11)	Right	36% (4/11)		100%
Width	Normal	100% (11/11)	Tight	0% (0/11)	Broad	0% (0/11)		
Infraction /outfraction L	None	36% (4/11)	Infraction	45% (5/11)	Outfraction	18% (2/11)		100%
Infraction/ outfraction R	None	45% (5/11)	Infraction	18% (2/11)	Oufraction	18% (2/11)		82% (9/11)
Middle 1/3 of the nose								
Deviation	None	45% (5/11)	Left	0% (0/11)	Right	45% (5/11)		91% (10/11)
Shape	Normal	82% (9/11)	Inverted V	18% (2/11)				100%
Hump (n.f.s.)	None	27% (3/11)	Present	73% (8/11)				100%
Saddle (n.f.s.)	None	100% (11/11)	Present	0% (0/11)				100%
Lower 1/3 of the nose								
Nasal tip								
Deviation	None	55% (6/11)	Left	0% (0/11)	Right	36% (4/11)		91% (10/11)
Shape	Normal	27% (3/11)	Bulbous	27% (3/11)	Bifid	27% (3/11)	Prominent 0% (0/11)	82% (9/11)
Projection	Normal	73% (8/11)	Underprojection	9% (1/11)	Overprojection	18% (2/11)		100%
Rotation	Normal	64% (7/11)	Underrotated	36% (4/11)	Overrotated	0% (0/11)		100%
Columella								
Septal luxation	None	55% (6/11)	Left	18% (2/11)	Right	27% (3/11)		100%
Width	Normal	82% (9/11)	Tight	0% (0/11)	Broad	18% (2/11)		
Length	Normal	100% (11/11)	Short	0% (0/11)	Long	0% (0/11)		
Aspect	Normal	73% (8/11)	Retracted	0% (0/11)	Col. Show**	18% (2/11)		91% (10/11)
Double break present	Present	82% (9/11)	Not present	18% (2/11)				100%

Table 4. External nasal deformity in Treacher Collins syndrome: outcomes of consensus of three independent raters (continued)

Nasal item							Consensus %*
Alar region							
Alar flaring L	None	100% (11/11)	Left	0% (0/11)	Right	0% (0/11)	100%
Alar flaring R	None	100% (11/11)	Left	0% (0/11)	Right	0% (0/11)	100%
Nares L	Normal	36% (4/11)	Slit shaped	45% (5/11)	Round	18% (2/11)	100%
Nares R	Normal	64% (7/11)	Slit shaped	36% (4/11)	Round	0% (0/11)	100%
Alar height L	Normal	55% (6/11)	High	27% (3/11)	Low	0% (0/11)	82%2 (9/11)
Alar height R	Normal	91% (10/11)	High	9% (1/11)	Low	0% (0/11)	100%
Basis							
Width (frontal view)	Normal	64% (7/11)	Tight	18% (2/11)	Broad	9% (1/11)	91% (10/11)
Width (caudal view)	Normal	81% (9/11)	Tight	9% (1/11)	Broad	9% (1/11)	100%
Other							
Nasofrontal angle	Normal	73% (8/11)	Deep	0% (0/11)	Flat	27% (3/11)	100%
Nasal length	Normal	81% (9/11)	Short	0% (0/11)	Long	9% (1/11)	91% (10/11)
Nasolabial fold L	Normal	64% (7/11)	Blunt	36% (4/11)			100%
Nasolabial fold R	Normal	55% (6/11)	Blunt	45% (5/11)			100%

n.f. s. : not further specified

* Consensus was reached when at least two-thirds of raters scored the specific deformity

** Columellar show

The item "total nasal appearance" was scored as "satisfied" in 81% (9/11); the two patients who previously underwent external rhinoplasty were the only dissatisfied patients. Compared with controls, satisfaction was significantly lower in the Treacher Collins group for the items nostril size (P=0.031), color of the nose (P=0.005), nasal position (P=0.014), and total nasal appearance (P=0.025) (Table 3).

External nasal deformity

The nasal items of all Treacher Collins patients were scored by the three independent raters. Median consensus rate of these three raters *per patient* was 96.6% (89.7-100%). Median consensus rate for all patients *per nasal item* was 100% (81.8-100%) (Table 4). Overall, the dorsal hump (cartilaginous and/or bony) was the most frequently found deformity (73%). Deviation was found most frequently in the upper 1/3 of the nose (55%). The aspect of the nasal tip was scored as bifid or bulbous in 55% and was underrotated in 36% of the patients (Table 4; Figure 3).

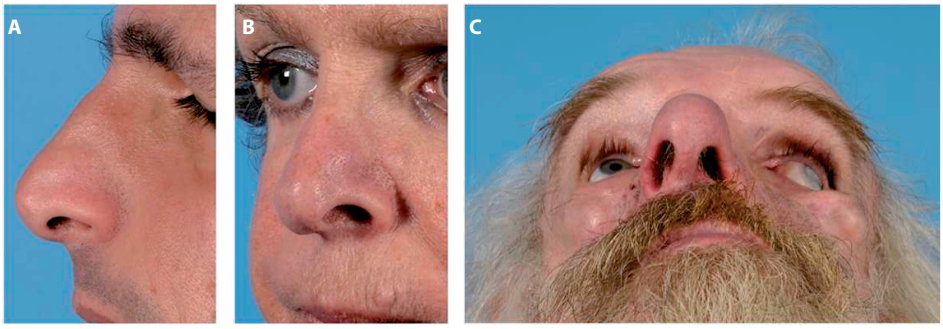

Figure 3. Most prominent external nasal deformities found in Treacher Collins syndrome
a-c: **a**: dorsal hump deformity, **b**: bifid tip, **c**: bulbous tip and septal luxation

Endonasal deformity

Endonasal deformities were found concerning the following constituents: turbinates, nasal septum, and nasal floor. In one of the two patients, turbinate deformity was directly related to previous surgery, whereas deformities *related* to the nasal septum (spurs, septal spines and/or deviations) were found in 100% (11/11) of the patients. Of all deformities, 82% (9/11) consisted of septal deviations which were dorsal (seven), caudal (one) and convex (one) deviations. The nine patients with septal deviations perceived their nasal obstruction to have the following frequency: "always" (one patient with severe obstructive sleep apnea), "mostly" (one patient with mild obstructive sleep apnea), "every now and then" (three), and "hardly ever" (four; of which one patient had mild obstructive sleep apnea). All these patients snored with the following frequency: "always" (four), "mostly" (one) and "now and then" (four). No current signs of rhinitis were

found in any of the patients. One of the two patients without septal deviation had previously undergone septoplasty. Spurs and septal spines were found in 7/11 patients and 4/11 patients, respectively (Table 2). One patient underwent choanal surgery; however, at the time of investigation this patient no longer showed choanal stenosis.

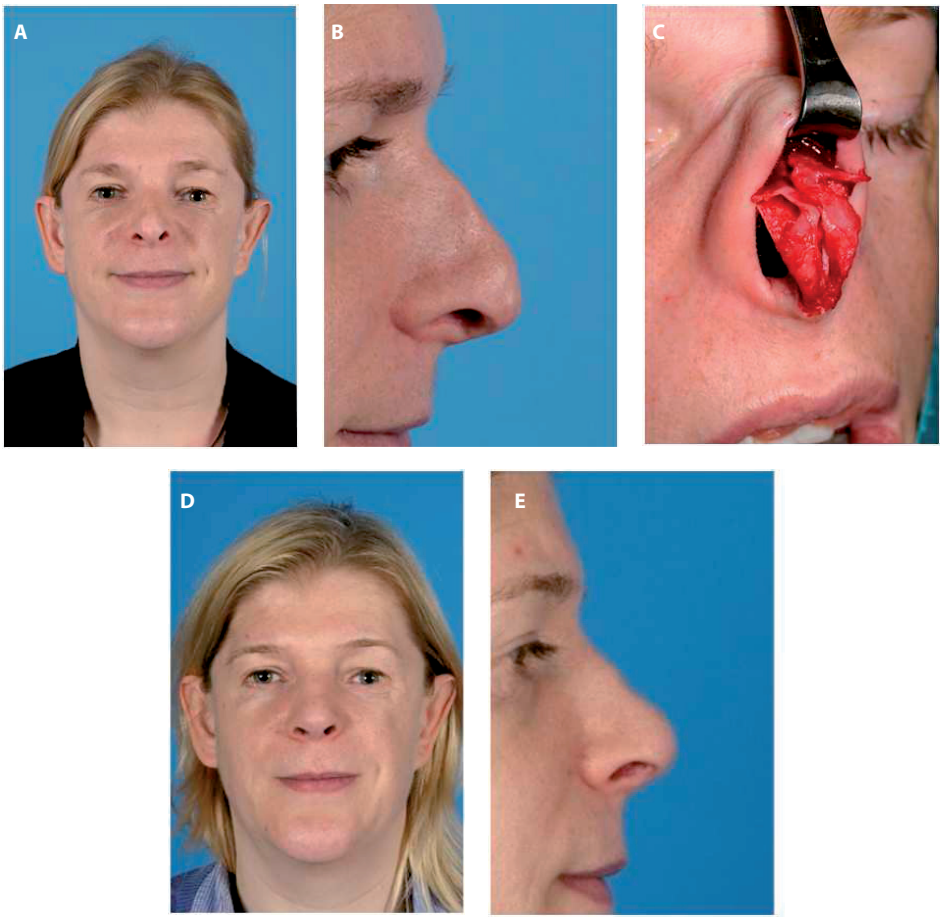

Figure 4. Bilateral clefting of the lateral alar cartilages in a patient with Treacher Collins syndrome. Preoperative (a-b), intra-operative (c) and postoperative photographs (d-e).
Preoperatively a bifid tip, a deviated osseous framework and a cartilaginous hump were found. The domes were not defined adequately and the tip was underrotated caused by low "hanging" medial crura. Intraoperatively, a hypoplastic alar rim and bilateral defect of the lateral alar cartilage suggested a bilateral cleft contributing to the deformed nasal tip and alar region; subsequently, this was corrected with alar rim grafts. The deviated osseous framework was corrected and the cartilaginous hump based on a septal ridge reduced, new domes were formed, *inter*domal sutures were placed, and a tongue in groove technique was used to reshape the region of the upper laterals.

Other congenital deformities included a broad divergent perpendicular plate of the ethmoid and a partial aplasia of the vomer. After the present study, one patient underwent a revision septorhinoplasty and, intraoperatively, a remarkable "clefting" of the bilateral alar cartilages was found (Figure 4).

DISCUSSION

This cross-sectional cohort study in patients with Treacher Collins shows that the main problems with nasal functioning were frequent snoring and diminished quality of phonation, as compared with controls. Although patients were less satisfied with nostril size, color, nasal position and total nasal appearance as compared with controls, they nevertheless reported to be "satisfied". The main external nasal deformities are the dorsal nasal hump, a deviated nose, and an abnormally shaped nasal tip. In addition, the main endonasal deformities are nasal septum deviations frequently associated with spurs.

External nasal deformity and satisfaction with nasal appearance

The most distinct external nasal deformities were the dorsal hump, an abnormally shaped nasal tip, and deviation of the upper to the lower one-third of the nose. Although Farkas et al. did not describe aspects of the tip, they found a protruded proximal part of the nose (possibly resembling the dorsal hump), and a relatively deep nasal root.[11] In the limited descriptive Treacher Collins literature, the nose is sometimes referred to as "prominent", and the facial profile as "convex" with a "droopy" tip.[10, 23] Probably called "prominent" due to a combination of the dorsal hump, exaggerated by a (usually) hypoplastic maxilla and orbitozygomatic complex, and a relatively deep nasal root. In addition, the posteriorly situated mandible and reduced cranial base angle give these patients a more convex facial profile.[23]

Underrotation was found in about one-third of the cases and possibly explained the "droopy" aspect in Treacher Collins. In addition, the nasal tip was frequently found to be bifid (subtle) and bulbous. This might suggest an embryological developmental origin in which the intermaxillary segment from the nasomedial processes forms structures including the primary palate, the nasal tip, crest of the nose and a portion of the nasal septum.[24] A cleft of the lateral alar cartilage (found in one of our patients), may contribute to the deformed lobule/nasal tip. In the present study, deformities (except for cleft palate) were found in all structures. The cartilaginous septal deviations found could cause deviations of the middle one-third and lower one-third of the nose.

Analysis of patient satisfaction showed that patients were significantly less satisfied compared with controls regarding nostril size, color of the nasal skin, nasal positioning and total nasal appearance. Nostril size, for example, was often scored as "slit like". All

patients were white skinned Caucasians and skin color was not scored by the panel. Therefore, there is no plausible explanation for the significant difference between the groups for this item. Moreover, taking into account that the medians/frequencies causing the *statistically* significant difference between the two groups are both high (corresponding with "satisfied" vs. "very satisfied" in the controls), this indicates that *clinically* the patients were in fact fairly (acceptably) satisfied. It is possible that patients focus less on specific nasal subunits and their relatively subtle deformities and much more on severe deformities (such as the eyelids and ears). Also, the *perceived* severity of the deformity generally correlates with a patient's level of acceptance/satisfaction with their facial appearance and this is largely determined by, e.g., education level, fear of negative evaluation of appearance, and self-esteem.[25-27]

We suggest performing –on indication- a rhinoplasty that includes osteotomies with in-fracture reduction of the skeletal and cartilaginous dorsal hump and removal of the cephalic portions of the lower laterals and on indication a septal cartilage graft to improve tip projection. In case of a significant septal deviation causing snoring or nasal obstruction this can be reconstructed at the same time.

Endonasal deformity and satisfaction with nasal functioning

The most frequently found deformity was the cartilaginous dorsal septal deviation (often accompanied by spurs and columellar septal luxation). Our detected prevalence of septal deviation is relatively high; however, in a "normal" population this prevalence is also high.[28-29] Results of the Nasal Appearance and Function Evaluation Questionnaire revealed that all patients with a septal deviation suffered from some degree of nasal obstruction; however, only two patients reported this to be "mostly" or "always". Dorsal septal deviations can cause the perceived nasal obstructions and may contribute to incompetence of the internal nasal valve area; also, caudal deviations can affect the external nasal valve area.[30] Compared with controls, patients scored snoring significantly more frequently. Explanations for nasal obstruction (other than septal deviation) were ruled out. In our adult patients, outcomes of snoring are similar to those in children with Treacher Collins and suggest that this is a consistent complaint for all ages; our results also match snoring frequencies in children with syndromic and complex craniosynostosis.[17, 31] Because snoring in Treacher Collins does not allow to distinguish between having/not having obstructive sleep apnea, a polysomnography is indicated.[17]

Although our patients frequently complained about the olfactory function, it was not different from the "standard" in our control group.[32] However, this was subjective determination of olfactory functioning. On the other hand, anosmia or hyposmia in Treacher Collins originating from a congenital sensorineural olfactory dysfunction is unlikely, as the olfactory placodes are derived from the neural plate and not from the neural crest.

In our patient group, only one was known with a choanal atresia/stenosis and, prior to the study, this patient underwent choanal surgery. In Treacher Collins syndrome, unilateral or bilateral choanal atresia is a rarely found and the exact prevalence is unknown.[33] However, one study estimated the prevalence to be about 11%.[12] Choanal atresia can be caused by a persistence of the nasobuccal membrane during embryologic development. However, a hypoplastic maxilla or affected surrounding structures of the choanae (e.g. vomer, palatal bone, medial pterygoid lamina) can also lead to stenosis/atresia of the choanae.[24] Interestingly, these structures can be affected due to a misdirection of neural crest migration with subsequent mesodermal flow; this mechanism might be involved in the etiology of Treacher Collins syndrome.[34]

In the present study, the quality of phonation was a considerable functional issue. It is known that speech problems (e.g., hyponasality, hypernasality and articulation errors) are important and can occur in ≤ 74% of patients with Treacher Collins syndrome.[12, 32]

Limitations

The main limitation of the present study is the low participation rate. Moreover, no objective external nasal measurements were performed; however, the nose was assessed by three independent raters. In addition, the nose was approached in a structured way, rather than measurements alone.

CONCLUSION

In this study group, although satisfaction with nasal esthetics is relatively good, the patients still suffer from the functional problems of snoring and impaired quality of phonation. A structured nasal ENT physical examination with nasal endoscopy could determine those aspects that require more attention during treatment. Septorhinoplasty can be performed at an adult age if the patient has a considerable esthetic wish and/or nasal obstruction combined with septal deviation. Special attention should be paid to dorsal hump reduction, correction of deviated external osseous framework, septoplasty, and correction of the shape of the nasal tip.

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GENERAL DISCUSSION: EVIDENCE-BASED MEDICINE, THE TREATMENT OF TREACHER COLLINS SYNDROME

Chapter VIII

Treacher Collins syndrome: a systematic review on evidence-based treatment and recommendations

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ABSTRACT

Background No reviews or guidelines are available on evidence-based treatment for the multidisciplinary approach in Treacher Collins syndrome (TCS). Aim is to provide an evidence-based review of multidisciplinary treatment of TCS based on levels of evidence and supported with graded recommendations.

Methods A systematic search was performed in PubMed, Web-of-Science, EMBASE, Cochrane Central (1985-January 2014). Included were clinical studies (with ≥5 TCS 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 for 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 (2-5)] were included. Conclusions and recommendations were consecutively extracted for the items: upper airway; the ear, hearing and speech; the eye, eyelashes and lacrimal system; growth, feeding and swallowing; the nose; psychosocial factors, and craniofacial reconstruction.

Conclusions This systematic review provides current evidence for the multidisciplinary treatment of TCS and makes recommendations for treatment. Although some topics are well supported, 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.

INTRODUCTION

Treacher Collins syndrome (TCS) is a rare congenital craniofacial condition.[1] TCS is an autosomal dominant disorder of craniofacial development with an estimated incidence of 1 in 50,000 live births.[2-4] Mutations in *TCOF1*, and in a smaller subset of TCS patients in *POLR1D* and *POLR1C,* are held responsible for the resulting phenotype; nevertheless, in some TCS patients no mutations within these three genes are detected.[4-6] The subsequent craniofacial morphogenesis has a wide range of inter- and intra-familial phenotypic variability.[7-8] Craniofacial deformities mostly consist 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 treatment challenging. Treatment nowadays is based on low levels of evidence consisting of mainly 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 an expert opinion.[13-19] Since 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 to assist physicians in their clinical decision-making and to explore the need for a multidisciplinary treatment approach in patients with TCS.

PATIENTS AND METHODS

A systematic search was performed in PubMed, Web of Science, EMBASE, Cochrane Central (1985- January 2014). The search term '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 (Figure 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 ((Treacher* NEXT/1 col*) OR (Franceschett* NEXT/1 syndrome*) OR (dysostos* NEAR/3 mandibul*)):de,ab,ti
For scopus: (("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 for Evidence-Based Clinical Practice Guidelines (Table 1 and 2).[20-21] Two panelists (RGP and MJSvL) reviewed each abstract separately. Lists of abstracts found per topic of interest (the overview studies and the seven topics as described

below) were critically reviewed between these two authors. Afterwards, 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 ≥ 5 TCS 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 < 5 TCS 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

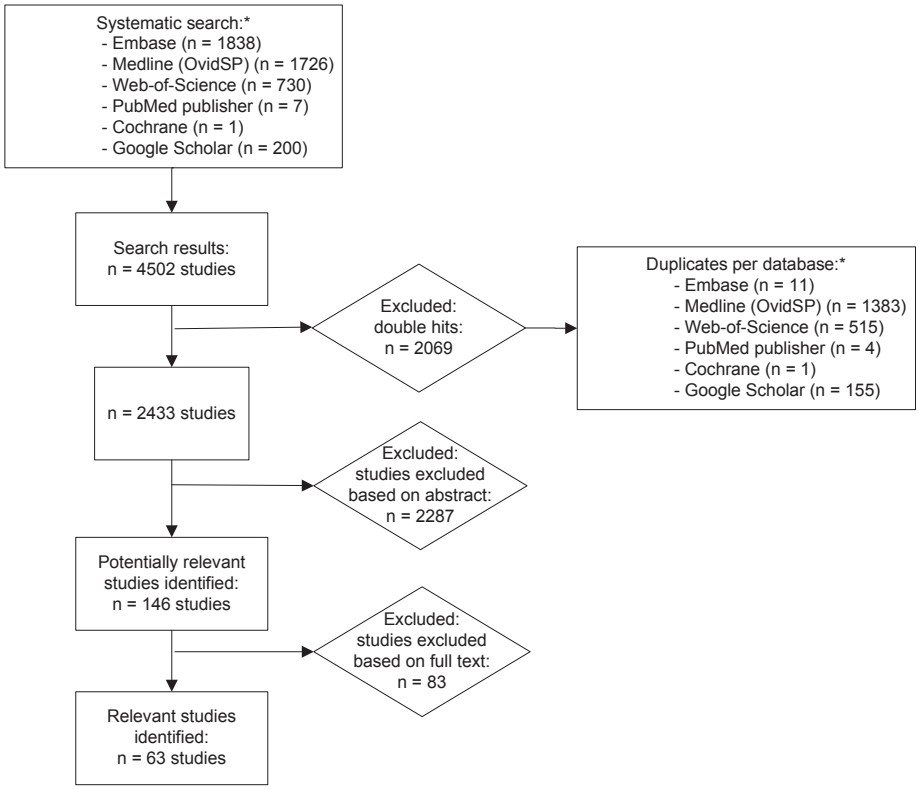

Figure 1. Flowchart of the systematic literature search for the present review.
*Databases searched consecutively

(A-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.

Table 1. Level of Evidenced-Based Medicine according to the American Society of Plastic Surgeons

Evidence rating scale for therapeutic studies	
Level of evidence	Qualifying studies
I	High-quality, multi-centered 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"
	Evidence rating scale for diagnostic studies
I	High-quality, multi-centered 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"
	Evidence rating scale for prognostic/risk studies
I	High-quality, multi-centered 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 2. Grades of recommendation according to the according to the American Society of Plastic Surgeons

Scale for grading recommendations			
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.

RESULTS

The literature search (after deduplication) yielded 2433 articles (Figure 1). Finally, 63 studies with different levels of evidence (range 2-5) were included. These results compiled "overview studies" addressing more than one topic and the seven topics of treatment (Table 3). No randomized controlled trials were found.

DISCUSSION

Upper airway

Obstructive sleep apnea (OSA) is a known frequent finding in congenital craniofacial syndromes. Also TCS patients suffer frequently from OSA. Only three papers report on the prevalence of OSA in TCS, each using different criteria (including a wide age range, and patients who already received treatment to improve breathing).[22-24] The reported prevalences were 25%,[25] 95% (11% tracheotomies)[23] and 46% (n=35; 6% tracheotomies),[22] respectively, despite several craniofacial surgeries related to the upper airway. OSA occurs in TCS children and adults[22] and there is no evidence for diminishing or changing prevalence and severity in the natural course of OSA with aging. The level of severity ranged from mild to severe; severe OSA syndrome was found in 25-41%.[22-24]

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Overview studies				
Thompson et al.[9]*	2009	Treacher Collins syndrome: protocol management from birth to maturity	n/a	4
Miller et al.[10]*	2006	Invited discussion: surgical treatment of Treacher Collins syndrome	n/a	5
Kobus et al.[11]*	2006	Surgical treatment of Treacher Collins syndrome	n/a	4
Marszalek et al[15]	2002	Clinical features, treatment and genetic background of Treacher Collins syndrome	n/a	4
Posnick et al.[14]*	2004	Treacher Collins syndrome: Current evaluation, treatment and future directions	n/a	5
Freihofer	2000	Variations in the correction of Treacher Collins syndrome	n/a	5
Posnick et al.[17]*	1997	Treacher Collins syndrome: perspectives in evaluation and treatment	n/a	5
Roncevic[19]*	1996	Mandibulofacial dysostosis: surgical treatment	n/a	4 and 5
Argenta et al.[16]*	1989	Treacher Collins syndrome: present concepts of the disorder and their surgical correction	n/a	5
Tulasne and Tessier[12]*	1986	Results of the Tessier integral procedure for correction of Treacher Collins syndrome	n/a	5
Upper airway				
Geirdal et al.[28]	2013	Association between obstructive sleep apnea and health-related quality of life in individuals affected with Treacher Collins syndrome	Obstructive sleep apnea, quality of life	2
Plomp et al.[22]	2012	Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity and cause	Obstructive sleep apnea, prevalence, etiology and therapy	2
Plomp et al. [27]	2012	Screening for obstructive sleep apnea in Treacher Collins syndrome	Obstructive sleep apnea, screening methods	2
Luna-Paredes et al.[31]	2012	Screening for symptoms of obstructive sleep apnea in children with severe craniofacial anomalies, assessment in a multidisciplinary unit	Obstructive sleep apnea, screening methods	4
Anton-Pachecho et al.[30]	2012	The role of bronchoscopy in the management of patients with severe craniofacial syndromes	Obstructive sleep apnea, Etiology	4
Akre et al.[23]	2011	Obstructive sleep apnea in Treacher Collins syndrome	Obstructive sleep apnea	2

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results (continued)

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Thompson et al.[9] *	2009	Treacher Collins syndrome: protocol management from birth to maturity	Obstructive sleep apnea, prevalence	4
Sorin et al.[26]	2004	Predicting decanulation outcomes after distraction osteogenesis for syndromic micrognatia	Obstructive sleep apnea, therapy	4
Sculerati et al.[24]	1998	Airway management in children with major craniofacial anomalies	Obstructive sleep apnea, therapy	2
Sher et al.[25]	1986	Endoscopic observations of obstructive sleep apnea in children with anomalous upper airways, predictive and therapeutic value	Obstructive sleep apnea, etiology	4
Hearing and speech				
Asten et al.[40]*	2013	Orofacial function and oral health associated with Treacher Collins syndrome	Speech problems, prevalence	2
Marsella et al.[45]	2011	Bone-anchored hearing aid (Baha) in patients with Treacher Collins syndrome, tips and pitfalls	Hearing, therapy	3
Thomeer et al.[44]	2010	Isolated congenital stapes ankylosis, surgical results of a consecutive series of 39 ears	Hearing, therapy	4
McDermott et al.[46]	2009	Quality of life in children fitted with a bone-anchored hearing aid	Hearing, therapy	3
Vallino[48]*	2006	The syndromes of Treacher Collins and Nager	Hearing and speech, therapy	5
Vallino-Napoli[35]*	2002	A profile of the features and speech in patients with mandibulafacial dysostosis	Speech problems	2
Takegoshi et al[41]	2000	Mandibulofacial dysostosis, CT evaluation of the temporal bones for surgical risk assessment in patients with bilateral aural atresia	Hearing, etiology	2
Marres et al. [42]	1995	Ear surgery in Treacher Collins syndrome	Hearing, therapy	2
Tayler et al.[43]	1993	Imaging of ear deformities in Treacher Collins syndrome	Hearing, etiology	2
Pron et al.[39]	1993	Ear malformation and hearing loss in patients with Treacher Collins syndrome	Hearing, etiology	2
The eye, eyelashes and lacrimal system				
Thompson et al.[9]*	2009	Treacher Collins syndrome: protocol management from birth to maturity	Visual disabilities, prevalence	2 and 5
Hertle et al.[50]	1993	Ophthalmic features and visual prognosis in the Treacher Collins syndrome	Visual disabilities, etiology	2
Wang et al.[51]	1990	Ocular findings in Treacher Collins syndrome	Visual disabilities, lacrimal system, eyelashes, prevalence, etiology	2

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results (continued)

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Bartley [52]	1990	Lacrimal drainage anomalies in mandibulofacial dysostosis	Lacrimal system, etiology	2
Growth, feeding and swallowing				
Asten et al.[40]*	2013	Orofacial function and oral health associated with Treacher Collins syndrome	Speech, feeding difficulties prevalence	2
Osterhus et al.[54]	2012	Salivary gland pathology as a new finding in Treacher Collins syndrome	Salivary secretion, ultrasound features, oral dryness, prevalence and etiology	2
Vallino-Napoli[35]*	2002	A profile of the features and speech in patients with mandibulafacial dysostosis	Speech problems, prevalence	2
The nose				
Plomp et al. **[56]	2014	Nasal sequelae of Treacher Collins syndrome	Endonasal deformity, external nasal deformity, nasal complaints, prevalence	2
Farkas et al.[58]	1989	Detailed morphometry of the nose in patients with Treacher Collins syndrome	External nasal deformity, prevalence	2
Psychosocial factors				
Plomp et al.[49]	2013	Long-term assessment of facial features and functions needing more attention in Treacher Collins syndrome	Satisfaction with facial features and functions, prevalence	2
Bemmels et al.[83]	2013	Psychological and social factors in undergoing reconstructive surgery among individuals with craniofacial conditions, an exploratory study	Psychological and social implications of craniofacial surgery, prevalence	4/5
Van den Elzen et al.[64]	2012	Assessing non-acceptance of the facial appearance in adult patients after complete treatment of their rare facial cleft	Acceptance of deformity, correlation with facial deformity, prevalence	2
Van den Elzen et al.[60]	2012	Adults with congenital or acquired facial disfigurement, impact of appearance on social functioning	Social functioning, predictors, etiology	2
Van den Elzen et al.[63]	2012	Defense mechanisms in congenital and acquired facial disfigurement, a clinical-empirical study	Coping mechanisms, etiology	2

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results (continued)

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Versnel et al.[62]	2012	Long-term psychological functioning of adults with severe congenital facial disfigurement	Long-term psychological functioning, predictors, prevalence ,etiology	2
Beaune et al.[61]	2004	Adolescents' perspectives on living and growing up with Treacher Collins syndrome, a qualitative study	Social functioning, prevalence	4
Barden et al.[65]	1988	The physical attractiveness of facially deformed patients before and after craniofacial surgery	Physical attractiveness, social functioning, treatment	2
Barden et al.[84]	1988	Emotional and behavioral reactions to facially deformed patients before and after craniofacial surgery	Social functioning, surroundings, treatment	2
Arndt et al.[59]	1987	Psychosocial adjustment of 20 patients with Treacher Collins before and after reconstructive surgery	Social functioning, effect of surgery, treatment	2
Craniofacial reconstruction				
Upper face				
Nikkhah et al.[85]	2013	Planning surgical reconstruction in Treacher Collins syndrome using virtual simulation	Surgical reconstruction, CT scan, Diagnosis	5
Nikkhah et al.[70]	2013	A classification system to guide orbitozygomatic reconstruction in Treacher Collins syndrome	Surgical reconstruction, diagnosis	5
Fan et al.[68]	2012	Optimizing the timing and technique of Treacher Collins orbital malar reconstruction	Surgical malar reconstruction, treatment	4
Thompson et al.[9]*	2009	Treacher Collins syndrome: protocol management from birth to maturity	Surgical reconstruction / treatment overall	5
Kobus et al.[11]*	2006	Surgical treatment of Treacher Collins syndrome	Surgical reconstruction overall, treatment	5
Miller et al.[10]*	2006	Invited discussion: surgical treatment of Treacher Collins syndrome	Surgical reconstruction overall, treatment	5
Posnick et al.[14]*	2004	Treacher Collins syndrome, comprehensive evaluation and treatment	Surgical reconstruction overall, treatment	5

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results (continued)

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Posnick et al.[13]	2000	Treacher Collins syndrome: Current evaluation, treatment and future directions	Surgical reconstruction overall, treatment	5
Posnick[17]*	1997	Treacher Collins syndrome: perspectives in evaluation and treatment	Surgical reconstruction overall, Treatment	5
Ronsevic et al.[19]*	1996	Mandibulofacial dysostosis: surgical treatment	Surgical reconstruction overall, treatment	4/5
Posnick et al.[67]	1993	Surgical correction of the Treacher Collins malar deficiency, quantitative CT scan analysis of long term results	Surgical malar reconstruction, treatment	4
Argenta et al.[16]*	1989	Treacher Collins syndrome: present concepts of the disorder and their surgical correction	Surgical reconstruction overall, treatment	5
Midface				
Kapadia et al.[69]	2013	Cephalometric assessment of craniofacial morphology in patients with Treacher Collins syndrome	Morphology, diagnosis	2
Saadeh et al.[72]	2008	Microsurgical correction of facial contour deformities in patients with craniofacial malformations: a 15-year experience	Microsurgical flap reconstruction, treatment	4
Saadeh et al.[71]	2006	A soft tissue approach to midfacial hypoplasia associated with Treacher Collins syndrome	Parascapular flap reconstruction, treatment	4
Freihofer[18]	1997	Variations in the correction of Treacher Collins syndrome	Surgical reconstruction overall, treatment	4
Roddi et al.[66]	1995	Treacher Collins syndrome, early surgical treatment of orbitomalar malformations	Orbitomalar reconstruction, treatment	4
Tulasne& Tessier[12]*	1986	Results of the Tessier integral procedure for correction of Treacher Collins syndrome	Maxillomandibular reconstruction, treatment	5
Lower face				
Terner et al.[75]	2012	An analysis of mandibular volume in Treacher Collins syndrome	Morphometry, diagnosis	2
Steinbacher et al.[76]	2011	Relation of the mandibular body and ramus in Treacher Collins syndrome	Morphometry, diagnosis	2

Table 3. Evidence on separate topics in Treacher Collins syndrome: the search results (continued)

First author	Year published	Title of article	Parameter(s) addressed	LEBM
Miloro[79]	2010	Mandibular distraction osteogenesis for pediatric airway management	Mandibular distraction, treatment	3
Shetye et al.[78]	2009	Documentation of the incidents associated with mandibular distraction, introduction of a new stratification system	Mandibular distraction, treatment	2
Heller et al.[80]	2006	Genioplasty distraction osteogenesis and hyoid advancement for correction of upper airway obstruction in patients with Treacher Collins and Nager syndrome	Genioplasty and hyoid advancement, treatment	4
Bresnick et al.[32]	2003	Increased fistula risk following palatoplasty in Treacher Collins syndrome	Palatoplasty, treatment	3
Stelnicki et al.[77]	2002	Long-term outcome study of bilateral mandibular distraction, a comparison of Treacher Collins and Nager syndromes to other types of micrognathia	Mandibular distraction, treatment	4

*This article is applicable and listed in two or more topics

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LEBM = Level of Evidenced-Based Medicine according to the American Society of Plastic Surgeons

Obstructions responsible for OSA are found in the whole upper respiratory tract, i.e. from nasopharyngeal to laryngeal level as observed through (sleep) endoscopy.[22, 26]

Screening for OSA in TCS based on the Epworth Sleepiness Scale in adults and the Brouillette score in children is unreliable; partially because a substantial part of the patients snore.[27-28] In general, questionnaires are unable to discriminate between snoring vs. OSA, or determine the severity of OSA.[29] In other studies the results were unclear, due to including several syndromes and/or not reporting syndrome-specific results (bronchoscopy[30] and screening questionnaires).[31]

Incidence of cleft palate is estimated at 23%.[32] There is no specific evidence that timing of cleft repair should be different from other cleft palate syndromes or non-syndromic cleft palate repair. A higher risk of palatal fistula is mentioned, although not much evidence is provided.[32] In a study researching several congenital craniofacial syndromes (including TCS) it is thought that the presence of a cleft palate reduces the probability of a tracheotomy.[24] Another study reported delayed palatal repair in some cases due to complicated airway management in TCS.[9] Although it is assumed that closure of the cleft palate narrows the airway, the exact effect on OSA of palate closure in TCS 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.[33-34]

In general, a tracheotomy necessary to secure the airway is reported in ≤ 41%.[22, 24, 35] Other options are CPAP or in selected cases a mandibular distraction osteogenesis. In mild OSA prone positioning could be considered as respiratory treatment (as in Pierre Robin sequence).[36]

Although one study showed a correlation between OSA severity and diminished health-related quality of life, it included few participants and facial deformity was an important confounding factor.[28]

The ear, hearing and speech

Although patients with TCS (and other craniofacial syndromes) can suffer from hearing loss, delay of appropriate treatment and, thus, hearing rehabilitation is still often encountered.[37-38]

Around 93-96% of TCS patients suffer from a unilateral or bilateral conductive hearing loss. Seven percent suffer from a mixed hearing loss.[35, 39] Hearing loss is moderate (41-55 dBHL) to moderately severe (56-70 dBHL),[35] the latter being reported in up to 65%.[9] Patients themselves often report hearing impairment (95%) and about 50% report communication difficulties.[40]

CT findings reveal complex, often combined deformities to both external auditory canal, middle ear cavity and inner ear. The external auditory canal is shown to be normal (0-15%), stenotic (28-31%) and atretic (54-72%). Middle ear cavity deformities are usually

symmetric and constitute of hypoplastic, ankylosed ossicles (33-82%) or missing ossicles (22-67%), particularly the malleus and incus.[39, 41-43] The inner ear is developed normally in most cases (78-100%),[39, 41, 43] the mastoid rarely shows pneumatisation.[41-43] The facial nerve sometimes runs a deviant course, complicating middle ear surgery.[40, 42-43]

Unfortunately, the outcome of reconstructive ear surgery is often disappointing and effective hearing improvement is achieved in only a minority.[42, 44]

The bone-anchored hearing aid (BAHA) offers significant hearing improvement compared with conventional bone-conduction hearing aids (in total 39 dB vs. 29 dB); also, its insertion has a low complication rate.[45] In addition, one study showed improved quality of life related to behavior, concentration, learning and development.[46] A banded hearing aid is an option for the first few years of life. In general, a BAHA should not be placed before 3 years of age.[47]

Speech development is frequently impeded in patient with TCS, although reported evidence is scarce.[9, 35, 48] One study showed that speech errors often consist of overlapping causes, related (in about 60%) to malocclusion, palatopharyngeal imcompetence (30%) and errors in the general articulatory/phonologic category or hearing loss(50%).[35] Hypernasality (palatopharyngeal imcompetence), hyponasality (restricted nasal cavities and/or choanal atresia), but also mixed resonance patterns, are found.[35] Patients are dissatisfied with their speech/quality of phonation compared to controls.[49]

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.[49] Moreover, the autologous reconstruction is impeded by a low hair implant and the limited options of reconstruction caused by unavailability of the temporofascial flap, if used earlier in pedicled bone grafts for the zygoma.

The 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%), amblyopia (33%), significant refractive errors (58%) and anisometropia (17%).[50] Another study found bilateral absence of the inferior lacrimal puncta (36%), cilia (50%), scleral show (50%), refractive errors (86%), regular astigmatism (36%) and absent lateral canthal tendon (64%).[51] Absent inferior lacrimal puncta, normal superior lacrimal puncta and intermittent or constant tearing were found in 71%.[52] One overview reported downslanting palpebral fissures in all and "visual disability" in around one third.[9] Although TCS patients are dissatisfied with the esthetic appearance of their eyelids, they are not dissatisfied with their vision compared to controls.[49] 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.[49] Colobomas need special attention at an early age from birth on because they form a potential threat to vision through corneal drying. A defect larger than one third of the eyelid margin indicates timely surgery.[53]

Growth, feeding and swallowing

Feeding issues are common in patients with craniofacial syndromes. However, direct evidence of orofacial dysfunctioning in TCS is scarce. TCS patients are generally rather thin, suggestion a feeding problem.[22] One study found reduced jaw opening (63%), malocclusion (94%), narrow hypopharynx (84%) and eating difficulties as reported by patients (68%) as well as dry oral mucosa (42%).[40] The latter may be partially explained by the salivary gland pathology, found in 48%. Dysplasia of the parotid and the submandibular gland was found in 29% and total aplasia in 19% of TCS patients. Over 50% had no parotid gland secretion and the orifice of Stenson's duct was often not detectable.[54]

The nose

Currently, there is limited evidence for endonasal and external nasal deformities and associated dysfunctional and esthetic sequelae. The clinical picture suggests a pollybeak deformity and a dorsal hump deformity.[9-11, 55] Main external nasal deformities were the dorsal hump (73%), external deviation (≤55%), bifid or bulbous tip (55%) and columellar septal luxation (55%).[56] In 82% a septal deviation was found, sometimes contributing to nasal obstruction.[56] A septorhinoplasty is advised from aged 17 years onwards.[13-14, 57] One study showed a prevalence of 11% of choanal atresia.[9] In 1989, Farkas et al. performed measurements (age range 6-21 years); in most patients the nose height and width was optimal, although a protruded proximal part of the nose and a relatively wide/deep nasal root was also found.[58] Another study reports patients who are relatively satisfied with the various esthetic subunits of the nose compared to a control group. The most significant functional problem was snoring.[27]

Psychosocial factors

Evidence for psychosocial problems is very limited.[59] Adults with congenital rare facial clefts appear to have a relatively "normal" long-term psychological functioning. However, stigmatization and insecurity about possible negative reactions of others can elicit stress and avoidance behavior.[60-61] Important predictors for long-term psychological functioning are fear of negative appearance evaluation, self-esteem and patients' satisfaction with facial appearance.[62] 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.[63] Interestingly, objective severity of the deformity is not a predictor for patients' acceptance of the deformity or for long-term psychological functioning. However, compared to a non-

affected population, TCS patients remain less satisfied about several facial subunits (i.e. ears, facial profile, eyelids and chin).[49] Congenital craniofacial patients less frequently have a partner or children and are prone to internalizing behavior problems.[62] 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.[64] Importantly, especially these functional problems frequently occur in TCS.[49] In mixed craniofacial groups, surgery seems to positively affect patients' attractiveness,[65] satisfaction with facial appearance[59] and reactions of their surroundings.[65]

Craniofacial reconstruction

Craniofacial reconstruction is the most challenging part of treatment in TCS. 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.[66-67] Disadvantage is resorption of calvarial bone grafts for zygomatic reconstruction, which occurs in almost all patients.[68]

The hypoplastic maxilla is positioned posteriorly in relation to the cranial base.[69] Techniques for correcting the midface hypoplasia are the Le Fort I (age > 16 years), Le Fort II 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[70] or lipofilling. Although limited, there is some evidence for a safe and reliable malar reconstruction using parascapular free flap transfer.[71-72] However, microvascular free flaps can be bulky, have a tendency to sag, and may require multiple revisions for thinning and resuspension as in, e.g. progressive hemifacial atrophy. Lipofilling can be a treatment of choice in these syndromes.[73] Inorganic implants might be an option, but may be as with inorganic implants in general, more prone to infection and dislocation.[74]

Lower face

The mandible in TCS is retrognathic: the ramus is short, the ramus body angle is more obtuse and the mandibular plane angle more steep, and a deep antegonial notch is often present.[75-76] There is evidence for safe mandibular lengthening at age 1-4 years with distraction osteogenesis[77] to correct the pediatric compromised airway resulting from the congenitally retrognathic mandible.[78-79] A small study (n=5) reported that genioplasty distraction osteogenesis combined with hyoid advancement might also be favorable in TCS, in case mandibular distraction fails to reduce the upper airway obstruction.[80] Patients cannot always be decannulated after mandibular distraction, probably due to multi-level

obstructions.[26] Throughout the years a thorough dental/orthodontic screening is necessary to monitor malocclusion and dental crowding. Orthodontic treatment may be indicated pre- and/or postoperatively regarding mandibular and/or maxillary surgery.[9, 13-14]

Grading systems

Some subjective grading systems have been described to grade TCS. Hayashi et al described a scoring system with eight criteria (facial features and the *TCOF1* mutation).[81] The second is the O.M.E.N.S. classification, as initially proposed for craniofacial microsomia indicating five major facial features.[82] A third, more recently proposed expert opinion based orbitozygomatic classification system indicates four types of severity and their advised reconstruction.[70] Although all these classification systems illustrate the variety and severity of the deformities, these classifications have never shown a predictive value with regards to functional problems and/or timing and type of treatment; therefore they are rarely used in clinical practice.

All together, main targets of the multidisciplinary treatment of TCS should be early recognition of OSA through a polysomnography and a thorough ENT physical examination to determine the level of upper airway obstruction. (Table 4 and figure 2) The results of these examinations should determine the next steps in treatment. In severe respiratory distress a nasopharyngeal tube could be temporarily an option followed by a tracheotomy. Prior to 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 to start treatment as soon as possible.

In addition, an ophthalmologist should be consulted to identify and treat (intra-) ocular deformities. There exist a considerable dissatisfaction with (residual) deformity after craniofacial surgery. Counseling of psychological sequelae and creating realistic expectations for the patient seems essential. Sufficient evidence on surgical reconstructions lacks to provide an *evidence-based* treatment protocol, but a proposed treatment algorithm was made for respiratory care. (Figure 2)

Because of the rarity of the syndrome it is recommended to centralize medical care of these patients in a craniofacial center nation/ statewide. This provides conjoined expertise of physicians and more possibilities for research to compare outcomes of different treatment modalities.

Table 4. Conclusions and recommendations for treatment of Treacher Collins syndrome

Topic	
Upper airway	Evidence rating scale*
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	Grade of recommendation**
A laboratory polysomnogram (type I) 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 a 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 months re-evaluation of respiratory distress and reconsider treatment	D
The ear, hearing and speech	
Conclusions	Evidence rating scale*
TCS patients mainly suffer from moderate to severe conductive bilateral hearing loss	II
BAHA implantation results in significant improvement of hearing	II
Due to 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	Grade of recommendation**
Starting at 3 months 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 years onwards) seems inevitable for appropriate hearing rehabilitation and precedes external ear reconstruction later on	B

Table 4. Conclusions and recommendations for treatment of Treacher Collins syndrome (continued)

Topic	
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 years	C
The eye, eyelashes and lacrimal system	
Conclusion	Evidence rating scale*
Refractive errors, scleral show, absent lateral canthal tendons, frequent tearing and colobomas frequently occur	II
Recommendations	Grade of recommendation**
An ophthalmologic screening at a young age (± 1 year) and regular follow-up is recommended	C
Indications for correction of eyelid deformities are imminent functional problems like 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	Evidence rating scale*
There is limited evidence for feeding and swallowing problems in TCS. A combination of orofacial anatomic deformities seems responsible for the reported eating difficulties	III
Recommendation	Grade of 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
The nose	
Conclusions	Evidence rating scale*
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	Grade of 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

Table 4. Conclusions and recommendations for treatment of Treacher Collins syndrome (continued)

Topic	
Psychosocial factors	
Conclusions	Evidence rating scale*
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 on 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	Grade of recommendation**
Creating realistic expectations concerning postoperative results is generally accepted, but seems especially applicable to congenital craniofacial patients	B
It is recommended to consult a psychologist around age 6-8 years 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	Evidence rating scale*
There is insufficient evidence for a standard surgical treatment of the craniofacial malformations in TCS	n/a
Recommendations	Grade of recommendation**
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 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

n/a = not applicable

* Level of Evidenced-Based Medicine according to the American Society of Plastic Surgeons

** Grades of Recommendations according to the American Society of Plastic Surgeons

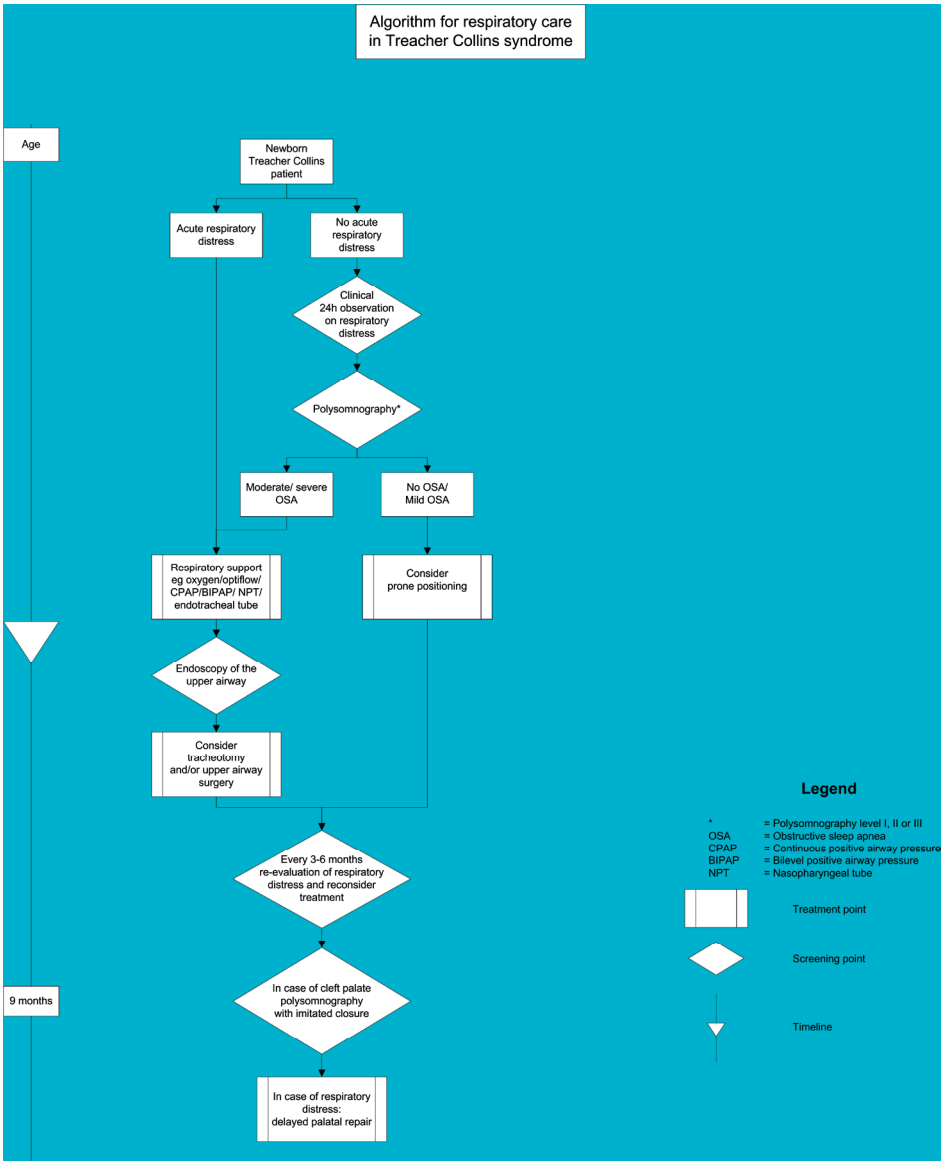

Figure 2.
Algorithm for respiratory care in Treacher Collins syndrome

Limitations

This systematic review is limited by the low evidence provided for treatment of TCS 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 TCS and makes recommendations for treatment. Although some topics are well supported, 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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SUMMARY / SAMENVATTING

Chapter IX

English and Dutch summary of the thesis: clinical implications of Treacher Collins syndrome

Hoofdstuk IX: Engelse en Nederlandse samenvatting van het proefschrift: klinische implicaties van het Treacher Collins syndroom

ENGLISH SUMMARY OF THE THESIS:

CLINICAL IMPLICATIONS OF TREACHER COLLINS SYNDROME

General introduction

In the general introduction (**chapter I**) of the thesis entitled "Clinical implications of Treacher Collins syndrome", the history, background, outline and aims of the thesis are described.

Treacher Collins syndrome (TCS) is a congenital craniofacial condition. It is estimated that four to five children with this syndrome are born every year in the Netherlands (estimated incidence 1:50,000). Little scientific attention has been paid to TCS due to the rarity of the syndrome. The severity and clinical consequences of the facial deformities can vary per patient. Deformities range from mild periorbital soft tissue defects, hypoplastic ears (both the auricle and the middle ear) to severe facial deformities of the mandible and zygoma leading to a severely compromised upper airway and obstructive sleep apnea (OSA). The assortment of deformities found in TCS lead to severe esthetic problems, but also to functional deficits, for example upper airway, hearing and feeding problems. The facial features of TCS are symmetric and it is assumed that men and women are affected equally.

This thesis aims to answer four clinical questions in TCS:

1) To determine the prevalence, severity, cause and screening of OSA and potential effects of OSA on oxidative stress and inflammation (chapter II, III and IV)
2) To determine which facial features, functions and psychosocial aspects need more attention during treatment in the long-term (chapter V and VI)
3) To determine external and endonasal deformity, and satisfaction with nasal functioning and appearance (chapter VII)
4) To provide recommendations for treatment by a systematic evidence-based review of multi-disciplinary treatment based on levels of evidence (chapter VIII)

Obstructive sleep apnea

Congenital craniofacial syndromes are associated with upper airway problems leading to OSA. Prevalence and severity of OSA vary between craniofacial syndromes. It is known that OSA occurs in TCS to a certain extent. However, scientific clinical evidence has been limited and difficult to obtain in this group, due to the rarity of the cases and the varying range in severity of phenotypic presentation of the disorder. In **chapter II** of the thesis the prevalence, severity and anatomical cause of OSA was determined in a cross-sectional cohort of 35 TCS patients (13 children). To determine prevalence and severity of OSA, an ambulatory polysomnography was used. In addition all upper

airway related surgical interventions were evaluated. In 11 patients an endoscopy of the upper airway was performed. OSA was diagnosed in TCS in 46% (41% in adults, 54% in children). Despite the fact that multiple TCS patients had undergone one or more upper airway related surgeries (38 surgical interventions in 17 patients), the prevalence of OSA was still high in children and adults. Endoscopic examination of the upper airway revealed obstruction at various anatomical levels. The most significant obstruction was found at the level of the oro/hypopharynx. OSA has shown to be an important problem in TCS patients considering the high prevalence and severity, which can persist even after upper airway surgery. Therefore polysomnography is recommended for screening for the presence and severity of OSA. In case of OSA, additional endoscopy of the upper airway is advised for determining the level(s) of obstruction and to guide treatment. This proposed work-up for OSA provides a base for individualized multilevel treatment, and will result in more adequate treatment of OSA in this population. When there are no surgical options for severe OSA in for example a multilevel severe obstructed airway and in young children, a non-invasive ventilation or continuous positive airway pressure should be considered as a treatment modality. In case of severe OSA and respiratory support fails, a tracheotomy is necessary.

The gold standard for screening for OSA is the poly(somno)graphy. This can be performed in hospital or in an ambulatory setting at home. To determine whether other tools for screening for OSA in TCS patients are useful, the value of other screening methods was explored. Therefore the aim of **chapter III** was to evaluate the accuracy of two established OSA questionnaires in children and adults with TCS. In children the Brouillette score was used. The Brouillete score is composed of three questions: the presence of apneas, breathing during sleep, and snoring. The total score is calculated using a formula (range of score -3.83 – 6.79) with the following classification: a score below -1 is defined as no OSA, a score between -1 and 3.5 as suggestive for OSA and a score > 3.5 as suspect for OSA. As cutoff for the classification OSA was -1 used. In adults the Epworth Sleepiness Scale was used. The Epworth Sleepiness Scale provides eight questions regarding hypersomnolence. The total score (range from 0 to 24) indicates significant hypersomnolence in eight individual situations during the day. A score ≥ 10, a score ≥ 16 indicates a high level of hypersomnolence. As cutoff for the classification OSA was used a score ≥ 10. Outcomes of the questionnaires were compared with the polysomnography results as described in chapter II. The total Brouillette score showed a low sensitivity (50%), specificity of 71%, and a low positive and negative predictive value (60% and 63% respectively). The Epworth Sleepiness Scale showed a low sensitivity (0%), a high specificity of 92% and a low positive and negative predictive value of 0% and 57% respectively. It can be concluded that these specific questionnaires are not useful for screening for OSA in TCS. By using these questionnaires the diagnosis OSA in TCS will be missed in a lot of patients. Possibly due to habituation to the nocturnal respiratory

pattern this questionnaire is not reliable. It is therefore recommended that all (newly) referred pediatric and adult TCS patients are screened for OSA with a polysomnography.

OSA is associated with additional oxidative stress and systemic inflammation. Oxidative stress can contribute to the initiation of atherosclerosis and vascular dysfunction; systemic inflammation is a predictor for future cardiovascular comorbidity and hypersomnolence. Until now it is unknown what the effect of OSA on oxidative stress and systemic inflammation is in congenital craniofacial deformities, this is the reason this was further explored in **chapter IV**. A cross-sectional cohort study was performed in patients in with TCS and syndromic craniosynostosis. Laboratory analyses were performed including malondialdehyde, tumor necrosis factor α (TNF-α), interleukine 6 (IL-6) and high sensitivity C-reactive protein (hCRP). Forty-eight patients were included. De Body Mass Indexes of the patients were normal (median (SD) 0,7 (-1.82 tot 2.48)) in children and 20.5 (15.2-29.4) in adults. OSA was diagnosed in 23 of the 48 patients; mild OSA in 16 and moderate/severe in seven patients. Neither oxidative stress nor systemic inflammation had a correlation with the severity of OSA. Only TNF-α was found significantly higher in both the OSA and non OSA group compared with the reference values of a normal population, median 15,1 pg/mL en 12,3 pg/mL respectively versus 4,05 (0,0- 8,1 pg/mL). The increased levels of TNF-α in both the OSA and non OSA group, cannot be explained by OSA; it might be possible that an unknown genetic origin is responsible for this finding. It can be concluded that no elevated levels were found for oxidative stress and systemic inflammation. This could be explained by a relative high prevalence of mild OSA in this group and the absence of an associated comorbidity in a "normal" population: obesity.

Long-term results of treatment

Patients with TCS are operated frequently for several facial deformities. One of the aims of treatment is satisfaction with the result of the operation. But do we reach our goals? How satisfied are patients with their facial features and functions after (surgical) treatment on the long term? Is there still a desire for further treatment? Not much is known about the answers to these questions in TCS, therefore this was explored (**chapter V**). A cross-sectional cohort study was performed in adults (23 TCS patients and 206 controls, all ≥ 18 years). A standardized questionnaire (adjusted Body Cathexis Scale) was used to detect differences between satisfaction with facial appearance and functions. Desire for further treatment of these items was questioned in TCS patients. For each patient an overview was made of all facial surgical interventions performed, the affected facial features and objective severity of the facial deformities. Patients were least satisfied with the appearance of the ears, facial profile and eyelids. Regarding functioning, patients were least satisfied with hearing and nasal patency. Residual deformity of the reconstructed facial areas remained a problem in mainly the periorbital area. The desire

for further treatment and dissatisfaction was high, predominantly for eyelid reconstructions. Another significant wish for further treatment existed for hearing improvement.

On the long term TCS adults are moderately satisfied regarding their facial appearance. Functional deficits of the face are shown to be as important as facial appearance. Particularly nasal patency and hearing are frequently impaired and require routine screening and treatment from intake onwards. Furthermore, correction of ear deformities and midface hypoplasia should be included in regular screening and the treatment protocol.

It is plausible that severe congenital craniofacial conditions are associated with psychological issues. Moreover, it can be questioned if so, whether differences exist between an acquired and a congenital facial deformity. In literature this is poorly understood. To determine the impact of these psychological issues in our patient group a study is performed as described in **chapter VI**. In this chapter long-term psychological functioning was assessed in three groups: a group with a severe congenital craniofacial deformity including TCS, a group with an acquired facial deformity and as comparison a non-facially disfigured control group. Differences between these groups regarding long-term psychological functioning were determined. Fifty-nine adults with severe congenital facial disfigurement, 59 adults with an acquired facial deformity in adulthood and 120 non-facially disfigured adults participated. Six questionnaires were filled out regarding long-term psychological functioning the Fear of Negative Appearance Evaluation Scale, Achenbach Adult Self-Report, Short-Form Health Survey, Rosenberg Self-Esteem Scale, Hospital Anxiety and Depression Scale and a visual analogue scale. Adults with severe congenital facial disfigurement had a relatively normal psychological functioning but appeared to be more prone to internalizing problems (over-control regarding emotions, emotions are focused inwards, for example social anxiety, anxiety in general and depression) than the control group. Compared with patients with an acquired facial deformity, the congenital group displayed fewer problems on the physical component summary (physical quality of life only, for example physical activity, work related problems and physical pain). Satisfaction with facial appearance, fear of negative appearance evaluation and self-esteem showed to be good predictors for several aspects of long-term psychological functioning with the exception of the physical component summary of quality of life. Improving satisfaction with facial appearance (by craniofacial surgery), enhancing self-esteem by early psychological support, or lowering fear of negative appearance evaluation may ameliorate the treatment of these patients.

The nose: endonasal and external nasal deformity and satisfaction with function and appearance

As described in chapter V, TCS patients are dissatisfied with their facial profile and complain about nasal obstruction. Although the nose is not the most prominent facial feature of TCS, it is generally considered a feature of TCS when deformed. In **chapter VII** external and endonasal deformity and satisfaction with nasal functioning and appearance was assessed. A cross-sectional cohort study was performed with 11 adult TCS patients and 151 controls. The Nasal Appearance and Function Evaluation Questionnaire as used earlier for assessing oncological resection and trauma, was filled out by the patients to determine satisfaction with nasal functioning and appearance. In all TCS patients external nasal deformities were scored on a predetermined scoring list by three experienced physicians in craniofacial surgery. Endonasal deformity was determined by standardized nasal endoscopy. Patients were relatively satisfied with the various esthetic nasal subunits. The most significant nose related functional problems were snoring and quality of phonation. The main external nasal deformities as scored by physicians were the dorsal hump (73%), external deviation (≤ 55%), the bifid or bulbous nasal tip (55%), and columellar luxation (55%). In 82% of the patients a septal deviation was found, often associated with spurs. The nose appeared to be frequently deformed and is considered a facial feature of TCS. Although the nose appears to be an underexposed feature of TCS to both patient and physician, possibly other more prominent facial features attract more attention. In summary, satisfaction with esthetics of the nose was fair, however, these patients suffer from the functional problems snoring and impaired quality of phonation. A structured nasal ENT physical examination with nasal endoscopy could determine aspects requiring more attention during treatment. Regarding the external nose, attention should be paid to dorsal hump reduction, correction of the deviated external osseous framework, a septoplasty and correction of the nasal tip shape.

Evidence-based medicine: the treatment of Treacher Collins syndrome

One of the aims of the thesis was to make recommendations for treatment of TCS. Until now no systematic review or clinical guideline is available based on sufficient level of evidence to make funded recommendations. Therefore **chapter VIII** was written, as last part of this thesis. This chapter is a systematic review with the aim to summarize the current evidence-based medicine for multidisciplinary treatment of TCS. In addition graded levels of recommendation were presented for treatment based on what nowadays is known.

A systematic search was performed in PubMed, Web-of-Science, EMBASE, Cochrane Central (1985-January 2014). Included were clinical studies (with ≥5 TCS 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 for Evidence-

based Clinical Practice Guidelines. Two panelists had reviewed each abstract separately and consensus was reached concerning article inclusion. Of the 2433 identified articles, 63 studies [level of evidence (2-5)] were included. Conclusions and recommendations were consecutively extracted for the items: upper airway; the ear, hearing and speech; the eye, eyelashes and lacrimal system; growth, feeding and swallowing; deformities of the nose; psychosocial factors and craniofacial reconstruction. Although some topics are well supported, especially the eye, eyelashes and lacrimal system speech, growth, feeding and swallowing and deformities of the nose lack sufficient evidence.

Main targets are early recognition of OSA through a polysomnography and a thorough ENT physical examination of the nose to determine the level of upper airway obstruction. The results of these examinations should determine the next steps in treatment. Moreover, more attention should be paid for the limited functions hearing and speech, these deficits should be recognized early.

In addition, an ophthalmologist should be consulted more often to identify and treat (intra-)ocular deformities. Feeding problems can be encountered early and followed up by a dietician and/or (prelingual) linguist. A structured ENT examination of the nose can determine deformed subunits of the nose and a wish for further nasal reconstruction can be evaluated. An nasal endoscopy could establish endonasal deformities leading to upper airway obstruction. There exist a considerable dissatisfaction with (residual) deformity after craniofacial surgery. Counseling of psychological sequelae and creating realistic expectations for the patient seems essential. Also on the topic of surgical reconstruction lacks sufficient evidence to provide in a full *evidence-based* treatment protocol.

Therefore, more research is necessary to compare outcomes of craniofacial surgical reconstruction, especially in the orbitozygomatic/ maxillary region. Because of the rarity of the syndrome it is recommended to centralize medical care of these patients in a craniofacial center nationwide. This provides conjoined expertise of physicians and more possibilities for research to compare outcomes of different treatment modalities. Until now, the most important limitation of craniofacial research is the low number patients available.

NEDERLANDSE SAMENVATTING PROEFSCHRIFT:

KLINISCHE IMPLICATIES VAN HET TREACHER COLLINS SYNDROOM

Algemene introductie

In de algemene introductie (**hoofdstuk I**) van dit proefschrift getiteld "Klinische implicaties van het Treacher Collins syndroom" worden de geschiedenis, achtergrond, en doelen van dit proefschrift beschreven.

Treacher Collins syndroom (TCS) is een aangeboren aangezichtsafwijking. Per jaar worden ongeveer vier tot vijf kinderen met dit syndroom geboren (geschatte incidentie 1:50.000) in Nederland. Door de zeldzaamheid van het syndroom is er relatief weinig medisch wetenschappelijke aandacht voor geweest. De ernst en de klinische consequenties van de aangezichtsafwijkingen verschillen per patiënt. Afwijkingen kunnen variëren van milde ooglidafwijkingen, hypoplasie van de oren (zowel externe oorschelp als middenoor) en zeer ernstige afwijkingen van mandibula en zygomata hetgeen kan leiden tot een ernstig bedreigde bovenste luchtweg en obstructief slaap apneu (OSA). Dit scala aan afwijkingen leidt tot esthetische maar ook functionele problemen, waaronder luchtweg- gehoor- en voedingsproblematiek. De aandoening is symmetrisch en komt bij mannen en vrouwen evenveel voor.

Doelen van dit proefschrift waren om in TCS:

1) Prevalentie, ernst, oorzaak en screening van OSA alsmede gerelateerde potentiële neveneffecten hiervan op oxidatieve stress en inflammatie vast te stellen (hoofdstuk II,III en IV).
2) Lange termijn resultaten van behandeling te onderzoeken en daardoor vast te stellen welke kenmerken en functies van het aangezicht alsmede welke psychosociale aspecten meer aandacht behoeven in de behandeling (hoofdstuk V en VI).
3) Uitwendige en endonasale afwijkingen van de neus vast te stellen, alsmede tevredenheid met functie en esthetiek (hoofdstuk VII).
4) Aanbevelingen voor multidisciplinaire behandeling te doen door middel van een systematic review gebaseerd op level of evidence (hoofdstuk VIII).

Obstructief slaap apneu

Congenitale craniofaciale syndromen zijn geassocieerd met bovenste luchtweg problematiek in de vorm van OSA. Prevalentie en ernst kunnen verschillen per syndroom. Het is bekend dat OSA in een bepaalde mate en ernst voorkomt in TCS. Echter, wetenschappelijk klinisch bewijs is beperkt en moeilijk te verkrijgen in deze groep vanwege de zeldzaamheid van de casus en de variërende ernst van de fenotypische presentatie van de aandoening. In **hoofdstuk II** is in een cohort van 35 patiënten met TCS (13 kinderen)

de prevalentie, ernst en anatomische oorzaak van obstructief slaap apneu (OSA) onderzocht. Een ambulante polysomnografie werd in een cross-sectionele studie verricht om de prevalentie en ernst van OSA te bepalen. Daarnaast werden alle soorten van chirurgie met betrekking tot de bovenste luchtwegen geëvalueerd. In 11 patiënten werd endoscopie van de luchtwegen verricht. OSA werd gediagnosticeerd in 46% van de TCS patiënten (41% in volwassenen en 54% in kinderen). Ondanks het feit dat veel patiënten al meerdere chirurgische ingrepen gerelateerd aan de bovenste luchtwegen hadden ondergaan (38 ingrepen bij 17 patienten) bleek in zowel kinderen als volwassenen de prevalentie van OSA nog hoog te zijn. Het endoscopisch onderzoek liet verschillende anatomische niveaus van obstructie zien. Het meest belangrijke obstructieniveau werd gevonden op het niveau van de oro/hypofarynx. OSA is een belangrijk probleem gezien de hoge prevalentie en ernst en wat kan persisteren ondanks chirurgie van de bovenste luchtwegen. Aanbevolen wordt om alle patiënten met TCS te screenen op aanwezigheid en ernst van OSA middels polysomnografie. In geval van OSA wordt aanvullende endoscopie van de bovenste luchtweg geadviseerd om het niveau van de luchtwegobstructie vast te stellen en om de behandeling te bepalen. Deze voorgestelde work-up voor OSA voorziet in een basis voor geïndividualiseerde multi-level behandeling en zal zorgen voor een adequatere behandeling van OSA in deze populatie. Indien er geen chirurgische behandelopties zijn voor ernstig OSA in bijvoorbeeld een multi-level ernstig geobstrueerde luchtweg en bij jonge kinderen, dan zal ademhalingsondersteuning met non-invasieve beademing of continue positieve druk ondersteuning noodzakelijk zijn. Bij zeer ernstige OSA waarbij het niet mogelijk is ademhalingsondersteuning toe te passen is een tracheotomie de behandeling.

De gouden standaard voor OSA screening is de poly(somno)grafie. Deze meting kan gedaan worden in het ziekenhuis of in de thuissituatie. Om te bepalen of er alternatieven zijn voor OSA screening werd ook het nut van andere screeningsmethoden bepaald. Derhalve was het doel van **hoofdstuk III** om vast te stellen in hoeverre twee veel gebruikte vragenlijsten ontworpen voor screening op OSA bruikbaar zijn bij kinderen en volwassenen met TCS. Bij kinderen werd de Brouillette score gebruikt. De Brouillette score bestaat uit een drietal vragen: de aanwezigheid van ademstilstanden, moeilijkheden met ademhalen tijdens het slapen en snurken. De antwoorden op de vragen leveren middels een formule een score op (range: -3.83 tot 6.79) met de volgende normering voor risico op OSA: een score van <-1 geen OSA, een score tussen -1 en 3.5 suggestief voor OSA, een score > 3.5 verdacht voor OSA. Als afkappunt voor classificatie op OSA werd -1 aangehouden. Voor volwassenen werd de Epworth Sleepiness Scale toegepast. De Epworth Sleepiness Scale bevat acht vragen die betrekking hebben op hypersomnolentie. De totaalscore van de vragen (range 0 tot 24) geeft een mate van hypersomnolentie in acht verschillende situaties gedurende de dag aan. Een score ≥ 10

geeft belangrijke hypersomnolentie aan, een score ≥ 16 ernstige hypersomnolentie. Als afkappunt voor classificatie op OSA werd een score ≥ 10 aangehouden.

De vragenlijsten werden vergeleken met de uitkomsten van polysomnografie zoals beschreven in hoofdstuk II. De Brouillette score toonde een lage sensitiviteit (50%), specificiteit 71%, en lage positief voorspellende waarde (60%) en negatief voorspellende waarde (63%). De Epworth Sleepiness scale toonde een lage sensitiviteit (0%), hoge specificiteit (92%) en lage positief voorspellende waarde (0%) en negatief voorspellende waarde 57%. Geconcludeerd kon worden dat specifieke vragenlijsten voor OSA screening niet zinvol zijn voor screening in patiënten met TCS. Bij veel patienten zal de diagnose OSA gemist worden als enkel deze vragenlijsten gebruikt zouden worden. Mogelijk speelt gewenning aan het ademhalingspatroon 's nachts hierin een oorzakelijke rol. Derhalve wordt aanbevolen om alle (nieuwe) verwezen kinderen en volwassenen met TCS op OSA te screenen middels een polysomnografie.

OSA is geassocieerd met een toename van oxidatieve stress en systemische inflammatie. Oxidatieve stress draagt bij aan de initiatie van atherosclerose en vasculaire dysfunctie; systemische inflammatie is een voorspeller voor toekomstige cardiovasculaire comorbiditeit en hypersomnolentie. Tot nu toe is nog onbekend wat het effect van OSA op oxidatieve stress en systemische inflammatie is in congenitale craniofaciale afwijkingen, derhalve werd dit in **hoofdstuk IV** onderzocht**.** Er werd een cross-sectionele cohort studie gedaan bij patiënten met TCS en syndromale craniosynostose. Diverse laboratorium bepalingen werden verricht om markers van oxidatieve stress en systemische inflammatie te bepalen (malondialdehyde (MDA), tumor necrosis factor α (TNF-α), interleukine 6 (IL-6) en high sensivity C-reactive protein (hCRP)). Er werden 48 patiënten onderzocht. De Body Mass Index van de patiënten waren normaal met een mediaan (SD) van 0,7 (-1.82 tot 2.48) in kinderen en 20.5 (15.2-29.4) in volwassenen. In 23 van de 48 patiënten werd OSA gediagnosticeerd; milde OSA bij 16 patiënten en matig/ernstig OSA bij zeven patiënten. De markers voor oxidatieve stress en systemische inflammatoire hadden geen correlatie met de ernst van OSA. Er werd enkel voor TNF-α een significant hogere waarde dan de referentiewaarden van de "normale populatie" gevonden, zowel in de OSA groep als de non OSA groep (mediaan respectievelijk 15,1 pg/mL en 12,3 pg/mL versus 4,05 (0,0- 8,1 pg/mL). De verhoogde TNF-α waarde in zowel de non OSA als OSA groep kan vooralsnog niet door OSA direct verklaard worden, mogelijk ligt hier een nog niet onderzochte genetische origine aan ten grondslag.

Geconcludeerd werd dat er geen verhoogde waarden werden gevonden voor de markers van oxidatieve stress en systemische inflammatie. Redenen hiervoor kunnen zijn de relatief hoge prevalentie van met name mild OSA in deze groep en de afwezigheid van een belangrijke geassocieerde comorbiditeit in de "normale" OSA populatie: obesitas.

Lange termijn resultaten van behandeling

Patiënten met TCS worden frequent geopereerd aan verschillende afwijkingen van het aangezicht. Doel van behandeling is onder andere dat de patiënt tevreden is met het resultaat van de operatie. Maar in hoeverre slagen we hier daadwerkelijk in? Hoe tevreden zijn patiënten nu precies op de lange termijn met welke uiterlijke kenmerken en functies van het aangezicht? En bestaat er nog een behandelwens? Omdat op het antwoord van deze vragen weinig bekend is werd dit onderzocht (**hoofdstuk V)**. Er werd een cross-sectionele cohort studie verricht bij volwassenen (23 TCS patienten en 206 controles, allen ≥ 18 jaar) waarin door middel van een gestandaardiseerde vragenlijst (adjusted Body Cathexis Scale) is gekeken naar verschillen qua tevredenheid met uiterlijk en functies van het aangezicht. Verder is er gekeken naar wensen voor verdere behandeling binnen het patiënten cohort. Voor elke patiënt werd een overzicht van alle aangezichtsoperaties gemaakt, de aangedane aangezichtsdelen en ernst van de afwijking gescoord. TCS patiënten waren het meest ontevreden over het uiterlijk van de oren, profiel van het gezicht en oogleden. Qua functie waren ze het meest ontevreden over de functie van het gehoor en de neuspassage. Restafwijkingen van de aangezichtsreconstructies werden met name genoemd in de peri-orbitale regio. Er was een aanzienlijke wens voor verdere behandeling en de ontevredenheid was groot aangaande de ooglidcorrecties. Er was ook duidelijk de wens om het gehoor te verbeteren.

Op lange termijn zijn TCS volwassenen matig tevreden over hun uiterlijk van het aangezicht en staan met name ook functionele problemen op de voorgrond; vooral neuspassage- en gehoorklachten zijn hierbij frequent aanwezig en vereisen een routine screening en behandeling vanaf de eerste poliklinische intake. Verder zullen correctie van afwijkingen van de oorschelp en midface hypoplasie opgenomen moeten worden in de reguliere screening en het behandelschema.

Het is aannemelijk dat ernstige congenitale afwijkingen vaker geassocieerd zijn met het ontstaan van psychologische problemen. Daarnaast is het de vraag of er een verschil in psychologisch functioneren is tussen een verworven of een congenitale aandoening van het gezicht. In de literatuur echter is dit weinig onderzocht. Om de impact van deze problemen te bepalen in onze patiëntencategorie is een onderzoek verricht wat wordt beschreven in **hoofdstuk VI**. In dit hoofdstuk werd lange termijn psychologisch functioneren bepaald in drie groepen: een groep met ernstige congenitale aangezichtsafwijkingen inclusief TCS, een groep met verworven aangezichtsafwijkingen en ter vergelijk een controle cohort zonder aangezichtsafwijkingen. Er is gekeken naar verschillen qua lange termijn psychologisch functioneren tussen deze groepen. Negenenvijftig volwassenen met een ernstige aangeboren afwijking, 59 met een verworven afwijking en 120 controle patiënten participeerden. Zes vragenlijsten werden ingevuld met betrekking tot het psychologisch functioneren: de Fear of Negative Appearance Evaluation Scale, Achenbach Adult Self-Report, Short-Form Health Survey, Rosenberg Self-Esteem Scale,

Hospital Anxiety and Depression Scale en een visual analogue scale. Volwassenen met een ernstige aangeboren afwijking hadden een relatief "normaal" psychologisch functioneren maar bleken meer vatbaar voor internaliserende problemen (overcontrole over emoties waardoor dezen naar binnen worden gericht, bijvoorbeeld sociale teruggetrokkenheid, angst en depressie) dan het niet aangedane controle cohort. Vergeleken met patiënten met een verworven aangezichtsafwijking, liet de congenitale groep minder problemen zien op de physical component summary (fysieke kwaliteit van leven, bijvoorbeeld lichamelijke activiteit, fysieke werkgerelateerde problemen en pijn). Tevredenheid met het uiterlijk, angst om negatief beoordeeld te worden door anderen en zelfvertrouwen bleken goede voorspellers voor verschillende aspecten van lange termijn psychologisch functioneren met als uitzondering de physical component summary van kwaliteit van leven.

Verbetering van tevredenheid van het uiterlijk (door craniofaciale chirurgie), vergroten van het zelfvertrouwen door vroegtijdige psychologische hulp en verminderen van angst om negatief beoordeeld te worden anderen, kan de behandeling van deze patiënten met ernstige aangeboren afwijkingen verbeteren.

De neus: endonasale en uitwendige afwijking en tevredenheid met functie en esthetiek

Zoals in hoofdstuk V beschreven staat zijn TCS patiënten ontevreden over het profiel van aangezicht en de neuspassage. Hoewel de neus niet tot de meest karakteristieke afwijking binnen TCS wordt gerekend, is er wel sprake over het algemeen van een kenmerkende afwijkende vorm van de neus.

In **hoofdstuk VII** worden zowel de uitwendige als ook de endonasale afwijkingen bestudeerd en daarnaast de tevredenheid met functie en uiterlijk van de neus onderzocht. Er werd een cross-sectionele cohort studie uitgevoerd bij 11 volwassen TCS patiënten en een controle groep van 151 patiënten. De Nasal Appearance and Function Evaluation Questionnaire zoals ontwikkeld en gebruikt bij neusreconstructies na oncologische resectie en trauma, werd door het patiënten cohort ingevuld om tevredenheid met uiterlijk en functie van de neus vast te stellen. In alle TCS patiënten werden uitwendige afwijkingen van de neus gescoord door drie ervaren specialisten op het gebied van craniofaciale chirurgie volgens een vaste scoringslijst. Endonasale afwijkingen werden vastgesteld door middel van een gestandaardiseerde nasendoscopie van de neus. Patiënten waren relatief tevreden met de verschillende esthetische kenmerken van de uitwendige neus. De belangrijkste aan de neus gerelateerde functionele klachten waren snurken en kwaliteit van de stem. De belangrijkste afwijkingen die gevonden werden door de specialisten: de dorsale hump (73%), uitwendige deviatie (≤55%), een bifide of plompe neuspunt (55%) en luxatie in de columella (55%). In 82% van de patiënten werd een septum deviatie gevonden vaak samengaand met een basale crista. De neus bleek

vaak afwijkend te zijn en behoort dan ook tot een karakteristieke afwijking voor TCS. De neus blijkt tot nu toe een relatief onderbelichte afwijking bij patiënt en behandelaar, mogelijk doordat de opvallendere andere aangezichtsafwijkingen meer de aandacht trekken. Samenvattend is de patiënttevredenheid met de esthetiek van de neus redelijk, maar patiënten ervaren met name problemen met snurken en beperkte kwaliteit van de stem. Een gestructureerd KNO onderzoek van de neus met nasendoscopie kan bepalen welke endonasale afwijkingen meer aandacht behoeven in de behandeling van TCS. Qua uitwendige neus zou er aandacht moeten zijn voor reductie van de dorsale hump, correctie van de uitwendige deviatie van de neus, een septumplastiek en correctie van de vaak afwijkende neustip.

Evidence-based medicine: de behandeling van Treacher Collins syndroom

Een van de doelen van dit proefschrift was om aanbevelingen te doen voor behandeling van TCS. Tot op heden zijn er geen systematische reviews of richtlijnen beschikbaar gebaseerd op voldoende wetenschappelijk bewijs om tot gegronde aanbevelingen te komen. Daarom werd als laatste onderdeel van dit proefschrift **hoofdstuk VIII** geschreven. Dit hoofdstuk is een systematische review met als de doel weer te geven wat de huidige *evidence-based medicine* is voor de multidisciplinaire behandeling van TCS. Tevens werden er gegradeerde aanbevelingen gedaan voor behandeling gebaseerd op datgene wat er tot nu toe bekend is.

Een systematische zoekactie werd uitgevoerd op PubMed, Web-of-Science, EMBASE, Cochrane Central (1985 tot januari 2014). Geïncludeerd werden klinische studies (met ≥ 5 TCS patiënten) gerelateerd aan therapie, diagnose of risico van gerelateerde comorbiditeit. Level of evidence werd gescoord van alle geïncludeerde studies volgens het systeem van de American Society of Plastic Surgeons for Evidence-based Clinical Practice Guidelines. Twee auteurs hebben alle abstracts beoordeeld en er werd consensus bereikt over de geïncludeerde studies.

Van de 2433 geïdentificeerde artikelen werden 63 studies (level of evidence 2-5) geïncludeerd in de studie. Conclusies en aanbevelingen werden vervolgens opgesteld voor de volgende onderwerpen: bovenste luchtweg; het oor, horen en spraak; het oog, oogleden en traanwegsysteem; groei, voeding en slikken; de neus; psychosociale factoren en craniofaciale reconstructie.

Er kan geconcludeerd worden dat voor sommige onderwerpen redelijk bewijs is, echter ontbreekt er met name voldoende bewijs voor de volgende onderwerpen: het oog, oogleden en traanwegsysteem; groei, voeding en slikken en afwijkingen van de neus.

Kernpunten zijn vroege herkenning van OSA middels een polysomnografie en een gedegen KNO onderzoek waarin de niveaus van de bovenste luchtweg obstructie worden bepaald. Deze onderzoeken dienen bepalend te zijn voor de behandelingsopties in het vervolgtraject. Daarnaast zal er meer vroegtijdige herkenning en aandacht

voor de beperkte functies van het gehoor en spraak moeten zijn. Ook zal een oogarts vaker geconsulteerd dienen te worden om oogafwijkingen vast te stellen en te kunnen behandelen. Voedingsproblemen kunnen vroegtijdig samen met een diëtist en/of (pre-verbale) logopedist behandeld en vervolgd worden. Een gestructureerd uitwendig KNO onderzoek van de neus kan bepalen wat afwijkend is aan de vorm van de neus en er kan geïnventariseerd worden of er een wens bestaat tot reconstructie. Een nasendoscopie kan endonasale afwijkingen vaststellen die tot luchtwegobstructie kunnen leiden. Er bestaat nog steeds een aanzienlijke ontevredenheid over de (rest) afwijkingen na aangezichtschirurgie. De gevolgen hiervan op psychologisch gebied alsmede het goed counselen van patiënten en reële verwachtingen creëren lijkt essentieel. Ook bij het onderdeel chirurgische reconstructies ontbreekt voldoende bewijs voor een volledig *evidence-based* behandelprotocol.

Derhalve is er meer onderzoek nodig om uitkomsten te vergelijken van craniofaciale chirurgische reconstructie, met name in de orbitozygoma/ maxilla regio. Omdat het een zeer zeldzame aandoening betreft verdient het aanbeveling om de behandeling landelijk te centraliseren in een nationaal craniofaciaal centrum. Dit biedt bundeling van expertise maar ook betere mogelijkheden voor wetenschappelijk onderzoek waarmee bijvoorbeeld verschillende behandelmodaliteiten en de resultaten daarvan onderzocht kunnen worden. Tot nu toe zijn met name de patiëntenaantallen de beperkende factor binnen craniofaciaal onderzoek.

Appendices

Gratitude/ Dankwoord

List of publications

PhD Portfolio

Curriculum vitae

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LIST OF PUBLICATIONS

1. Versnel SL, **Plomp RG**, Passchier J, Duivenvoorden HJ, Mathijssen IMJ. Long-term psychological functioning of adults with severe congenital facial disfigurement.
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2. **Plomp RG,** Joosten KFM, Wolvius EB, Hoeve LJ, Poublon RML, van Montfort CAGM, Bredero-Boelhouwer HH, Mathijssen IMJ. Screening for obstructive sleep apnea in Treacher-Collins syndrome.
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3. **Plomp RG**, Bredero-Boelhouwer HH, Joosten KFM, Wolvius EB, Hoeve LJ, Poublon RML, Mathijssen IMJ. Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity and cause.
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4. **Plomp RG,** Versnel SL, van Lieshout MJS, Poublon RML, Mathijssen IMJ. Long-term assessment of facial features and functions needing more attention in Treacher Collins syndrome.
J Plast Reconstr Aesthet Surg. 2013 Aug;66(8):e217-26.

5. Driessen C, **Plomp RG,** van der Spek PJ, Ince C, Kulik W, Mathijssen IMJ, Joosten KFM. Is there an effect of obstructive sleep apnea syndrome on oxidative stress and inflammatory parameters in patients with craniofacial anomalies?
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6. **Plomp RG,** Mathijssen IMJ, Moolenburgh SE, van Montfort CAGM, van der Meulen JJNM, Poublon RML. Nasal sequelae of Treacher Collins syndrome.
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7. **Plomp RG,** Van Lieshout MJS, Joosten KFM, Wolvius EB, van der Schroeff, MP, Versnel SL, Poublon RML, Mathijssen IMJ.
Treacher Collins syndrome: a systematic review on evidenced-based treatment and recommendations.
Revisions submitted Plast Reconstr Surg.

PhD PORTFOLIO

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary
Summary of PhD training and teaching activities

Name PhD student: Raul Galeano Plomp
Erasmus MC Department:
Department of Plastic and Reconstructive Surgery
Research School: n/a

PhD period: 2009-2015
Promotor: Prof.dr. I.M.J. Mathijssen
Supervisors: Dr. K.F.M. Joosten and
Dr. S.L. Versnel

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- CPO minicursus Methodologie van Patiëntgebonden Onderzoek	2012	8/0.3
- BROK Course attendance	2011	8/0.3
- Biomedical English Course: writing and communication	2008	112/4
Research skills		
- NIHES PhD course: Survival analysis for clinicians	2012	20/0.7
- NIHES PhD course: Regression analysis	2011	20/0.7
- NIHES PhD course: Biostatistics for clinicians	2010	20/0.7
- NIHES PhD course: Introduction to clinical research	2009	20/0.7
In-depth courses (e.g. Research school, Medical Training)		
- Course on Evidence Based Practice, Oxford University, Oxford, UK	2012	20/0.7
International conferences:		
Oral presentations and co-authored abstracts		
- ENT scientific meeting September 2013 Rotterdam: Oral: *Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity, cause and screening*	2013	20/0.7
- X World Congress on Sleep Apnea Sleep Respiratory Disorders and Snoring, Rome, Italy: Oral: *Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity, cause and screening*	2012	20/0.7
- X World Congress on Sleep Apnea Sleep Respiratory Disorders and Snoring, Rome, Italy: Abstract: *Oxidative stress, systemic inflammation and sympathic inflammation in patients with craniofacial anomalies*	2012	20/0.7
- Bi-annual Scientific Meeting Dutch Society of Otorhinolaryngology (KNO) Groningen: Oral: *Obstructive sleep apnea in Treacher Collins syndrome: prevalence, severity, cause and screening*	2011	20/0.7
- Craniofacial Scientific Meeting Sophia Erasmus MC Rotterdam: Oral: *Inflammatory parameters and oxidative stress in Treacher Collins syndrome and syndromic craniosynostosis*	2011	20/0.7
- Annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC): Oral: *Long-term results satisfaction with facial appearance and functioning*	2011	20/0.7
- Scientific Meeting department of Plastic and Reconstructive Surgery, Erasmus MC Rotterdam: Oral: *Clinical implications of Treacher Collins syndrome*	2011	20/0.7

- International Society of Craniofacial Surgery (ISCFS) XIV Biennial International Congress, Livingstone, Zambia: Abstract: *Long-term results satisfaction with facial appearance and functioning*	2009	20/0.7
- Annual Meeting Dutch Society of Cleft Palate and Congenital Deformities (NVSCA), Tilburg: Oral: *Treacher Collins syndrome and obstructive sleep apnea: prevalence and severity*	2009	20/0.7
- International Society of Craniofacial Surgery (ISCFS) XIII Biennial International Congress, Oxford: Abstract: *Treacher Collins and obstructive sleep apnea*	2009	20/0.7
- Bi-annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC) Utrecht: Oral: *Treacher Collins syndrome and obstructive sleep apnea*	2009	20/0.7
Seminars and workshops		
- Bi-annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC), Utrecht	2012	8/0.3
- Bi-annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC), Haarlem	2011	8/0.3
- Bi-annual Scientific Meeting for General Surgery (NVVH), Ede	2010	8/0.3
- Bi-annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC), Maastricht	2009	8/0.3
- Annual Meeting Dutch Society of Cleft Palate and Congenital Deformities (NVSCA), Nijmegen	2008	8/0.3
- Benelux Meeting for Plastic, Reconstructive and Aesthetic Surgery 2008	2008	8/0.3
- Congress Wound Healing and Wound Treatment, Rotterdam	2007	8/0.3
- Bi-annual Scientific Meeting Dutch Society of Plastic Surgery (NVPC) Utrecht	2007	8/0.3
Organised conferences		
- Scientific meeting General Surgery, Region IV, Rotterdam	2014	56/2
- Congress wound healing and wound treatment, Rotterdam	2007	8/0.3
Grants		
- Nuts Ohra Foundation Grant: Treacher Collins syndrome	2010	112/4
- Stichting Hoofdzaak (former Carolien Bijl Foundation)	2010	
Other		
- MEC-2012-135 Approval Paper METC, Erasmus MC	2012	112/4
- MEC-2008-402 Approval Paper METC, Erasmus MC	2008	112/4
2. Teaching activities		
Lecturing		
- 3rd year minor "From head to hands" practicum: suture techniques	2011	14/0.5
- 3rd year minor "From head to hands": Hand anatomy, introduction to plastic surgery	2011	14/0.5
- 2nd year medicine students practicum anatomy: clinical implications of hand anatomy	2011	14/0.5
- 3rd year college Craniofacial surgery: Treacher Collins syndrome	2010	7/0.3
- 3rd year minor Craniofacial surgery: author study assignment "zelfstudieopdracht": Treacher Collins syndrome	2010	14/0.5
Supervising practicals and excursions		
- Supervision microsurgery course: skills lab Erasmus MC	2011-2012	28/1
Supervising Master's theses		
- None		

ABOUT THE AUTHOR

Raul Galeano Plomp was born November 15, 1984 in Bogotá, Colombia. In his first year of life he moved to the Netherlands. After finishing his high school gymnasium 'Camphusianum' in 2003, he started medical studies at Erasmus University Rotterdam and graduated in May 2010. He started his residency in surgery at the Albert Schweitzer Hospital, Dordrecht in 2010 (dr. P.W. Plaisier and dr. R.J. Oostenbroek).

As a medical student, and also during his internships, he performed research at the department of Plastic and Reconstructive Surgery which could be continued after receipt of a grant in 2011 for two years (prof. dr. I.M.J. Mathijssen, dr. S.L. Versnel and dr. K.F.M. Joosten). This research focused on the clinical implications of a rare congenital craniofacial syndrome: Treacher Collins syndrome.

After this period he worked as a resident in ENT at the Erasmus MC, Rotterdam from 2012 to 2013 (dr. R.M.L. Poublon and prof. dr. R.J. Baatenburg de Jong) and as a resident in surgery at the Sint Franciscus Gasthuis, Rotterdam in 2014 (dr. G.H.H. Mannaerts and dr. T.M.A.L. Klem). Here, the choice was made to apply for the surgery training program which he started with enthusiasm in January 2015 at the Máxima Medical Center in Veldhoven/Eindhoven (dr. R.M.H. Roumen, dr. M.R.M. Scheltinga and drs. M.H.M. Bender) and Maastricht UMC (prof.dr. L.P.S. Stassen).

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