BMJ Case Reports

TITLE OF CASE

Long term treatment outcomes from a patient's perspective with Treacher Collins Syndrome

SUMMARY

The management of patients with Treacher Collins Syndrome (TCS) is complex and involves many different specialists within multidisciplinary teams (MDT). The treatment pathway extends from birth well into adulthood and is associated with a heavy burden of care. Due to the extensive nature of the interaction with these patients, MDT members have opportunities to provide enhanced patient centred care and support.

This case report provides an overview of the current knowledge of the aetiology of TCS, the management of these patients and provides a unique perspective from one of the co-authors who has TCS and reports on his treatment experiences and long-term treatment outcomes.

By having a better understanding of the impact of TCS and treatment provided, MDT members can not only provide improved clinical treatment but also offer improved patient experiences for those with craniofacial anomalies in particular an increased awareness of the psychosocial challenges they endure.

BACKGROUND

Treacher Collins syndrome (TCS) (OMIM 154500) is a rare disorder with an incidence of only 1:50,000 live births.[1] Other names of this condition include Franceschetti-Zwahlen-Klein syndrome, Treacher Collins-Franceschetti syndrome, mandibulofacial dysostosis, and zygoauromandibular dysplasia. The gene responsible for most cases of TCS is *TCOF1*. Through several studies of families with TCS and candidate gene analysis, Dixon and colleagues[1,2,3] gradually concluded that the TCS locus was linked to markers in the chromosomal location of the gene to the long arm of chromosome 5, specifically 5q32-33.1 The protein product of *TCOF1* is the nucleolar phosphoprotein Treacle.[4] *TCOF1* was shown to be expressed in the embryonic neural folds and in the developing branchial or pharyngeal arches at critical morphogenetic stages. Mutations within *TCOF1* cause defects in the structure and function of Treacle resulting in a truncated protein that is detrimental to craniofacial development. Faulty Treacle and RNA polymerase activity lead to metabolic oxidative stress and massive neuroepithelial apoptosis, in turn causing a significant deficiency of neural crest cells for complete formation of the branchial arch 1 and 2 derivative craniofacial bones and tissues. While mutations in *TCOF1*[5] are responsible for most cases of TCS, there are three other genes more recently implicated in rarer forms of the syndrome, *POLR1B[6]*, *POLR1C* and *POLR1D.* Mutations in these three genes lead to craniofacial cartilage hypoplasia and cranioskeletal defects characteristic of TCS.

The British surgeon and ophthalmologist Edward Treacher Collins first described the essential traits of the syndrome back in 1900.[7] Treacher Collins Syndrome has a wide phenotypic variation from

extremely mild to severe malformations. The most common clinical features of TCS are illustrated in Figure 1 and noted in Table 1.

Table 1. Common clinical features of Treacher Collins Syndrome

Eyes	Downward slanting of the eyes and colobomas (absence of tissue or notching) of the outer third of the lower eyelid, hypertelorism
Ears	Abnormalities of the external and middle ear often leading to conductive deafness
Mandible	Small mandible which in severe cases can lead to breathing difficulties; Class II skeletal pattern often requiring orthognathic correction; abnormalities of the temporomandibular joints
Maxilla	Hypoplasia of the zygomatic bones
Oral	Cleft palate, palatopharangeal incompetence contributing to speech difficulties, class II malocclusion, anterior open bite, dental anomalies including tooth agenesis, ectopic eruption, and enamel defects

Upper airway obstruction due to the retrognathia and associated anatomical features is the most serious, and potentially fatal complication of TCS as illustrated in Figure 2. Complications resulting from the upper airway obstruction include choking, impaired respiration, difficult intubation and airway placement, and sleep-disordered breathing, and can lead to early death perinatally, postnatally, and any other time throughout life.[8]

As with other craniofacial anomalies the rehabilitation of a patient with TCS is coordinated and staged within a multidisciplinary team and numerous surgical and non-surgical management is tailored to the extent of the deformities involved.[9-12] These patients and their families often experience a range of emotional and psychological issues associated with the TCS abnormalities and its treatment.[13] A summary of typical treatment pathway (as experienced by the co-author) presented in Table 2 lists the range and complexity of clinical procedures that are commonly undertaken.

Table 2. Treatment pathway for Treacher Collins Syndrome -as experienced by the patient (co-author)

Age	Management	Surgical Intervention
Birth	Emergency transfer to neonatal intensive care unit (NICU)	Emergency tracheostomy
Neonate-8 months	Management of airway obstruction and feeding – failure to thrive	
3 years 1 month	Primary cleft palate repair	Primary palate repair with attempted closure of fistula 3 months later
4 years	Failed anaesthesia for dental treatment and need for resuscitation	
4 years 8 months	Decannulation of tracheostomy and failed closure of tracheostoma	Decannulation

5 years 4 months	Unsuccessful post-decannulation closure of tracheostoma (eventually achieved closure)	Tracheostoma post-decannulation and temporary tracheostomy tube placement
7 years 3 months	Initial surgical management of TCS anomalies (palatal fistula and mandibular retrognathia) by multiple-speciality craniofacial team	1) Attempted repair of palatal fistula by tongue flap (with accidental dehiscence of flap postoperatively) 2) Initial mandibular augmentation with bilateral split osteotomies with intermaxillary fixation for 2 months postoperative with temporary tracheostomy
8 years 1 month	Reconstruction of absent lower orbital rims and zygomatic arches and first stage earlobe reconstruction of microtia	1) Reconstruction of lower orbital rims and zygomatic arches by rib grafts and wires 2) First stage earlobe reconstruction by bone graft
8 years 6 months	Second stage of earlobe reconstruction of microtia	Second stage microtic earlobe reconstruction by pelvic bone and groin skin grafts
9 years 1 month	Surgical dental procedure (placement of crowns) and palatal obturator for persistent fistula	Placement of multiple crowns and abutments for a prosthodontic obturator appliance under GA
9 years 4 months	Third stage microtic earlobe reconstruction	Third stage microtic earlobe reconstruction with bone grafts
10 years 9 months	Attempted earlobe reconstruction with failed anaesthesia	Attempted fourth stage microtic earlobe reconstruction, aborted due to failed intubation
11 years 1 month	Near fatal food choking incident requiring emergency medical intervention (nonsurgical); the first of several such emergencies to occur over lifetime	
11 years 3 months	Mandibular advancement and augmentation	Bilateral mandibular osteotomies with screw plates and intermaxillary fixation for 2 months with temporary tracheostomy over same period
11 years 11 months	Implantation of magnetic bone conduction hearing aid	Implantation of bone conduction hearing aid with magnetic plate on left mastoid
12 years 2 months	Maxillary augmentation and second attempt at palatal fistula	1) Le Fort I maxillary osteotomy with plates, intermaxillary fixation and temporary tracheostomy for 2 months 2) Tongue flap for closure of palatal fistula, flap left in place for 2 months
13 years 3 months	Final stage microtic earlobe reconstruction	Microtic earlobe reconstruction by bone and skin grafts
14 years (continued through 19 years)	Initiation of pre orthognathic surgery orthodontic treatment with upper and lower fixed appliances	
16 years 8 months	Final stage mandibular and TMJ reconstruction due to condylar and glenoid fossa defects	Bilateral mandibular osteotomy and condylectomy, reconstruction of condyles with bilateral costochondral grafts, intermaxillary fixation and temporary tracheostomy for 2 months

17 years 3 months	Final stage maxillary reconstruction	Revision Le Fort 1 maxillary impaction osteotomy; “soft” intermaxillary fixation with elastics on existing orthodontic appliances for 2 months
17 years 11 months-18 years	Two-part ophthalmic and facial contour implant surgery; management of postoperative infections	1) Placement of bespoke contour implants (bilateral malar, and chin) 2) Shortening of right eye muscle 3) Surgical debridement and drainage of postsurgical infection of right implant after 1 month postoperatively
19 years	Completion of active orthodontic management and placement of retainers	
19 years 3 months	Biopsy for suspected bone neoplasm	Biopsy of right side of mandibular body (found to be scar tissue from previous mandibular surgeries)
20-21 years	Repeated occurrences of infection of malar contour implants placed at 17 years requiring surgical management of infections	Repeated debridement/drainage of left and right malar implants, culminating in removal of right malar implant, due to repeated postoperative infection
28 years 5 months	Bone anchored hearing aid (BAHA) implant	Placement of BAHA screw and abutment on right mastoid
29 years 5 months	Diagnosis of severe obstructive sleep apnoea (OSA) and initiation of permanent CPAP treatment	
42 years	Second BAHA implant	Placement of BAHA screw and abutment on left mastoid with removal of previous magnetic plate implant
42 years	Removal of two upper second molars for placement of bruxism mouth guard	

Of note are the considerable challenges associated with inadequacy of the airway and general anaesthetic intubation as well as the need for repeat treatment episodes. In addition to the activities undertaken illustrated in Table 2 the patient (co-author) also received extensive speech therapy, which was initiated at age 3, but he received only limited professional psychological counselling despite experiencing prolonged bullying and teasing which intensified when attending middle school (and was not ameliorated until secondary school).

CASE PRESENTATION

The patient (co-author), upon his birth with severe Treacher Collins syndrome, required immediate transfer to a neonatal intensive care unit in a paediatric hospital and underwent an emergency tracheostomy, which ultimately remained in situ for the first 5 years of life. For the first eight months of life, the patient was under management of failure to thrive and respiratory distress. Primary cleft palate repair was undertaken at 3 years, however, an oronasal fistula remained. Dental procedures at ages 3 and 9 including placement of crowns and abutments proved difficult and dangerous due to difficult airway management for anaesthesia. Repeated attempts were made to decannulate and close the patient’s tracheostomy; it was not successfully accomplished until age 5.

From ages 7-18, under the care of two multidisciplinary craniofacial teams, the patient had multiple

operations including multiple orthognathic surgeries (involving multi-staged mandibular rotation, advancement, and TMJ reconstruction as well as multi-staged maxillary advancement), tongue flaps for closure of the persistent palatal fistula, reconstruction of both orbits and zygomatic arches, multiple stages of microtic earlobe reconstruction, eye muscle surgery, and bespoke malar and chin contour implants. The patient also had multiple bone conduction hearing aid implants (at ages 11, 28, and 42).

At age 14, the patient began orthodontic treatment for dental crowding and anterior open bite malocclusion with functional fixed appliances, upper and lower, in preparation for the final stages of orthognathic surgery he underwent from ages 16-17 (final stage mandibular and TMJ reconstruction at age 16 and final stage maxillary advancement via Le Fort I at age 17). Almost all orthognathic procedures required a temporary tracheostomy and intermaxillary fixation for 2 months postoperatively to preserve the airway, immobilize the jaws, and allow soft or liquid feeding during healing. At age 19, the patient's orthodontic treatment was completed, and retention begun. However, in subsequent years, the patient has experienced relapse of both the orthodontic and orthognathic treatment (Figure 3). This has led to continuing masticatory and airway difficulties including severe obstructive sleep apnoea (OSA), for which he is in CPAP treatment.

From the outset, the patient has had extreme difficulty with induction of general anaesthesia due to severe upper airway obstruction secondary to glossoptosis resulting from persistent mandibular retrognathia, as well as abnormally small oral and nasal cavities. When a tracheostomy was present, anaesthesia was administered via that route. Ultimately, the issue of difficult-airway anaesthesia has been best addressed by awake fibre-optic intubation (with an ENT surgeon on call should emergency tracheostomy be required), after failure of previous approaches including mask induction and standard laryngoscopic intubation. The patient's aforementioned orthodontic and orthognathic relapse has also progressively worsened his upper airway obstruction and ultimately led to his diagnosis of severe OSA requiring CPAP. The patient has also had a lifelong problem with food choking sometimes requiring emergency medical attention, due to persistent masticatory difficulties and the upper airway obstruction.

Besides the medical and surgical challenges attending his TCS, the patient also had to deal with psychosocial issues, beginning with relinquishment by his biological parents at birth for foster and adoptive placement. Fortunately, the patient had good foster and adoptive families to care for his medical and psychosocial needs. As mentioned already, the patient was fitted with bone conduction hearing aids from infancy, enabling him to hear despite his bilateral anotia and auditory canal atresia. With a cleft palate, oronasal defects, mandibular micrognathia and retrognathia, and an obstructed airway, the patient's speech was severely impaired, requiring intensive individual speech therapy from ages 3-6. In primary school, from ages 6-15, he had speech therapy with an in-school speech therapist. At age 9, he attended a speech therapy summer camp.

The patient first faced bullying in primary school, which intensified in middle school. Bullying caused severe emotional trauma for him; however, little psychological help was made available. The patient was seen by a counselling psychologist for a short period at age 14, who was unable to draw him from a hardened shell created as protection from the emotional and psychological abuse of bullying. The patient was even enrolled in a karate class for a time, which also failed to instil self-confidence. The patient had already been in multiple primary and middle schools in attempts to find a school where he would be accepted, but it was not until yet another school transfer, for high school, where he finally found acceptance and an atmosphere where he could begin the years-long recovery. The patient ultimately was able to pursue an educational and career path focusing on the study and research of craniofacial anomalies and craniofacial sciences, culminating in the achievement of a PhD in craniofacial sciences. The

patient continues to build a career combining craniofacial scientific research and public engagement for craniofacial anomalies awareness and acceptance.

OUTCOME AND FOLLOW-UP

The case study of this patient (co-author) illustrates not only the need for collaboration and interaction between the multidisciplinary craniofacial team in planning a comprehensive treatment strategy for restoration of physical function (breathing, speech, and mastication), but also the need to address the individual patient's aesthetic desires and respond to psychosocial problems attending life with Treacher Collins syndrome.

Although there have been advances in new technologies and techniques the tendency for treatment relapse remains high for patients with TCS. The combination of the original anatomical defects, the distortions associated with restricted craniofacial growth and scarring associated with repeat surgery makes the retention of treatment changes more difficult. Unfortunately, for this patient the considerable orthodontic and orthognathic relapse over an extended period has resulted in compromised masticatory and breathing function.

DISCUSSION *Include a very brief review of similar published cases*

Treacher Collins syndrome is a rare disorder of craniofacial development which is characterised by bilateral symmetric structural anomalies within the first and second branchial arches. Differential diagnosis includes acrofacial dysostosis which include similar craniofacial features observed in TCS but with the addition of limb defects. These include Nager syndrome and Miller syndrome as well as more recently identified conditions such as acrofacial dysostosis, Cincinnati type [14]. Oculo-auriculo-vertebral spectrum (OAV) disorders including hemifacial microsomia and the Goldenhar syndrome variant are rare disorders that affect similar craniofacial structures but are usually asymmetric with less malar bone hypoplasia [15]. A diagnosis of TCS is based upon a detailed patient history, full clinical evaluation and identification of physical characteristics.

Of particular interest to those providing care for patients with TCS include the mandibular and maxillary abnormalities with associated poor dental and occlusal relationships, which lead to mastication and speech problems and serious airway compromise. Whilst both surgical and nonsurgical treatments are intended to restore function in patients with Treacher Collins syndrome, including speech, chewing, and breathing, they also serve to restore a normal aesthetic appearance to the face. Orthognathic correction often involves combined Le Fort 1 and mandibular bilateral sagittal split osteotomies. Distraction osteogenesis and genioplasties can be undertaken for greater mandibular advancements and support of the airway [16]. These orthognathic movements can be technically challenging due to the magnitude and direction of surgical movements required to establish facial balance and projection. In addition, there are challenges associated with soft tissue deficiency, previous surgical scarring and limited bone stock which also increases the complexity of fixation [12]. Long term retention is required as there is an increased risk of both surgical and orthodontic relapse [17] as experienced in this case report. Each individual with Treacher Collins syndrome has different psychosocial and aesthetic desires, along with different functional and clinical needs. Accordingly, each patient needs staged co-ordinated treatment plans tailored individually and commitment for long term follow up.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

The management of patients with TCS is associated with a complex and extended treatment pathway

Staged, co-ordinated surgical and non-surgical treatments are undertaken by the MD craniofacial team

Patients with TCS have challenging psychosocial, aesthetic, functional and clinical needs

Despite best efforts there is a risk of long-term relapse of treatment gains, the most significant relate to compromised masticatory and airway function

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FIGURE/VIDEO CAPTIONS

Figure 1. The cranioskeletal defects characteristic of Treacher Collins syndrome. Mandibular micrognathia, retrognathia, maxillary and malar hypoplasia, absent TMJ, incomplete zygomatic arches and orbits. (Hand drawn by Dr Francis Smith, from personal medical history)

Figure 2. Upper airway obstruction in Treacher Collins syndrome is caused by retrognathia (the mandibular border is drawn in dashed lines) pushing the tongue posteriorly into the oropharyngeal airway. (Hand drawn by Dr Francis Smith, from personal medical history)

Figure 3. The patient's (co-author) current occlusion indicating a return of the excessive anterior openbite, arch malalignment with associated difficulties including severe obstructive sleep apnoea and poor masticatory function. Note tongue flap tissue for closure of persistent palatal fistula. (NB. All photographs published in Handbook of Orthodontics 1st Edition, Martyn T. Cobourne and Andrew T. DiBiase Chapter 13, page 394 Copyright Elsevier, 2010)

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