Clinical spectrum of Treacher Collins syndrome

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ABSTRACT

Treacher Collins syndrome (TCS) is the most common of the human mandibulofacial dysostosis disorders. It is an autosomal-dominant disorder of the craniofacial development occurring between the fifth and the eighth weeks of embryonic development with an incidence of 1/50,000 live births, range between 1–40,000 and 1–70,000.

We present here the various clinical, radiographical and other diagnostic findings of the TCS to correlate the clinical assessment with the diagnostic imaging and review the various investigations and management options being carried out to improve their facial deformity.

Keywords: Bite force, missing zygomatic arch, TCOF1, Treacher Collins syndrome.

Treacher Collins syndrome (TCS) is the most common of the human mandibulofacial dysostosis disorders. It is an autosomal dominant disorder of the craniofacial development occurring between the fifth and eighth weeks of embryonic development with an incidence of 1/50,000 live births, range between 1–40,000 and 1–70,000.^{1,2}

Although the condition was first described in 1846 by Thompson, it was named after E Treacher Collins, who described the condition in 1900. The first extensive review of the condition was detailed by Franceschetti and Klein, 1949, who used the term mandibulofacial dysostosis to describe its clinical features.³

Symmetrical and bilateral involvement with clinical features like (1) abnormalities of the external ears, atresia of the external ear canals and malformation of the middle ear ossicles resulting in bilateral conductive hearing loss; (2) lateral downward sloping of the palpebral fissures, frequently with coloboma of the lower eyelids; (3) hypoplasia of the mandible and zygomatic complex, and (4) presence of cleft palate in TCS.³ These patients may present with chronic obstruction of the upper airways, micrognathia, tongue posture impairment, pharyngeal hypoplasia, laryngeal and tracheal narrowing with respiratory obstruction and obstructive sleep apnea syndrome.¹

Goldenhar syndrome, Nager's dysostosis and Miller's syndrome are among its differential diagnoses.⁴ The purpose of this research is to present the father and son as TCS

to correlate the clinical assessment with the diagnostic imaging and review the various investigations and management options.

MATERIALS AND METHODS

A 42-year-old man and his 17-year-old son (Figure 1) presented to the outpatient clinic for their dental treatment. The father presented with a convex facial profile with a

Figure 1 The photograph of a father and his son (frontal view) showing the classical features of Treacher Collins syndrome.

prominent nose over a retruded chin. His eyes were deformed with a downward obliquity of the palpebral fissures, temporal notching of the lower lids, strabismus and bilateral coloboma of the lower eyelids. He presented with a malformed right ear, which was half the size of the left. He had a nasal tone in his voice. His intelligence level was found to be low. Oral examination revealed poor oral hygiene which had been the cause for previous multiple extractions. He presented with a high arched palate. His orthopantomograms clearly showed bilateral elongated mandibular condyles and styloid processes, broad and short coronoid process, deep antegonial notches and short ramal lengths. Other than that, the temporomandibular joint anatomy was normal. Lateral cephalogram revealed bowing of the inferior border of the mandible.

Computed tomography (CT) scan demonstrated that nearly all facial bones were hypoplastic including zygomatic arch, mandible and external ear canals. Hypoplastic mandible presented a picture of midface protrusion while malar hypoplasia resulted in a diminished contour over the cheeks. CT examination for the right ear revealed a hypoplastic mastoid. Cochlea was present, but the external auditory canal and the middle ear were not formed. An ossicular chunk was present which could not be delineated. Membranous labyrinth was rudimentary. On the left side, there were again fused ossicles, with incus fused to the malleus (Figure 2A). However, the middle ear and the membranous labyrinth were well formed. Eustachian tube was bilaterally similar. Hearing was impaired. The CT also revealed missing inferior turbinate, the presence of a single nasal cavity and thickened left lateral nasal wall (Figure 2B). The level of the right maxillary sinus was lower than that on the left. Mucosal hypertrophy was seen on both the sides. The mandibular condyles were elongated bilaterally while the coronoid process was broad and short. Other than that, the temporomandibular joint anatomy as revealed on the CT was normal. However, the CT revealed deficient zygomatic arches bilaterally.

Magnetic resonance imaging (MRI) demonstrated bilateral masseter muscles originating from the temporalis muscle and the fascia in the absence of the zygomatic arches and inserting at the mandibular angle. The right masseter muscle and the parotid gland were hypoplastic as compared with the left. It also showed maxillary as well as sphenoidal sinusitis and an empty sella.

The son was severely hypoplastic on the right side of the face and presented with malformation of the auricular pinna, antimongoloid slant of both eyes. He had unilateral absence of the right auricle except for the lobule. Hearing was impaired but intelligence was normal. He also presented with a high arched palate with Class II malocclusion. His orthopantomogram showed normal mandibular condyles and styloid

processes, but broad and short coronoid process, deep antegonial notches and short ramal lengths. The anatomy of the temporomandibular joint was normal. Lateral cephalogram also revealed bowing of the inferior border of the mandible.

Figure 2 The computed tomography scan showing (A) fused ear ossicle, (B) single nasal cavity, and (C) missing right zygomatic arch.

His CT scan revealed rudimentary canal and a fused ossicular chunk. The maxillary sinus had more volume on the right, and the floor of the sinus was lower than that on the left. The right inferior turbinate was hypertrophic. Although both nasal cavities were present, the nasal septum was deviated toward the left. The anatomy of the temporomandibular joint was assessed using CT and was found normal on the right side but showed a flatter glenoid fossa on the left; 3D CT demonstrated missing zygomatic arches bilaterally (Figure 2C). The MRI revealed similar origin of the masseter muscle in the absence of the bilateral zygomatic arches as seen in his father. There were maxillary, sphenoid as well as ethmoid sinusitis and an empty sella.

Cephalometric analysis showed high mandibular plane angle, suggesting a downward growth pattern and deficient anteroposterior growth; while unaffected siblings had nearly normal values. Cant of the occlusal plane was also high in both the affected members.

The son was planned for the reconstruction of both zygomatic arches to establish the anteroposterior projection on a stable base. Bicoronal incision was used to expose both the zygomatic arches. The masseter muscle was seen to originate bilaterally from the temporal fascia. The cortico-cancellous iliac crest graft was harvested and fixed with a titanium manipulate and screws to the remaining zygomatic arch. Healing was uneventful with a pleasant result. The father refused to undergo any surgery for facial correction.

Bite force when measured in the affected father and son demonstrated lower values, more so in the posterior region. As the muscles originated from the temporalis muscle and fascia and not from the zygomatic arches, the chewing forces were justified to be low (Table 1).

The other siblings were two males, aged 14 and 10 years, respectively, completely normal, and had no features of this syndrome.

DISCUSSION

Treacher Collins syndrome shows an autosomal-dominant inheritance with variable expressivity. Classic findings include ear abnormalities, antimongoloid slanting of the palpebral fissures, temporal lower eyelid coloboma, a paucity of the eyelashes medial to the defect, malar and mandibular hypoplasia with a receding chin.⁵ Mostly, these present with normal intelligence, but may show hearing loss⁶ and genital anomalies.

A case series of seven Brazilian TCS patients, aged 4–38 years, presented the typical features with malocclusion in all, but anterior open bite in only three patients, while none with a cleft palate.⁷ Cephalometric analysis, in both of our cases, revealed mandible and midface to be short in the anteroposterior plane; obtuse mandibular plane angle, high antegonial notch and a retruded chin. Anatomy of the temporomandibular joint in our cases demonstrated some morphological alterations with changes in the mandibular dynamics and bite force.

The etiology of the facial defects in the TCS is unknown. More than 60% of patients have no positive family history and are thought to arise as a result of *de novo* mutation.⁶ Experimental and embryological evidence suggests that abnormal neural crest migration as early as 4 months gestation may be related to the defects of TCS. Genetic defect responsible for TCS maps to the long arm of chromosome 5 causing a complete absence of the embryonic malar bone centers or their outgrowth, or hypoplasia of the bones or parts of the bones after development.⁶ Treacher Collins syndrome locus has been mapped to chromosomes 5q31.3–32. Treacher Collins syndrome results from mutations in the *TCOF1* gene, which contains 26 exons and encodes a 1411 amino acid protein named *treacle*, interacts with an upstream binding factor (UBF) and affects the transcription of the ribosomal DNA gene. The highest levels of *TCOF1*

Table 1 Profile analysis and bite force measurements of the entire family members

Cephalometric analysis	Affected father	Affected son	Unaffected sibling 1	Unaffected sibling 2	Normal values
Facial angle	65	71	89	90	82–95
Angle of convexity	30	27	8	5	–8.5–10
AB plane angle	–12	–13	–6	–3	–9–0
Mandibular plane angle	62	48	25	28	17–28
Y-axis	85	76	60	55	53–66
Inter-incisal angle	126	122	128	130	130–150
Cant of occlusal plane	37	30	10	8	1.5–14
Bite force (Kg)	Affected father	Affected son	Unaffected sibling 1	Unaffected sibling 2	Normal values (Kg)
Anterior	4.2	25.8	17	19	10.2–15.3
Posterior left	3	13	33	34	30.6–40.7
Posterior right	Missing	15	35	36	30.6–40.7

expression are observed in the crests of the neural folds immediately prior to fusion and in the first pharyngeal arch.

Immunofluorescence labeling shows the treacle and the UBF to colocalize at specific nucleolar organizer regions and cosegregate within the nucleolar caps of the actinomycin d-treated HeLa cells. Biochemical analysis shows the association of the treacle and the UBF with chromatin.

Recent research has unveiled a successful avenue for its therapeutic intervention and prevention. When contemplating the reconstructive options for TCS, consideration should be given to complex the interplay between the growth of the craniofacial region and the possible effects of early surgery on further growth.⁸

Treating craniofacial malformations through comprehensive, well-coordinated and integrated strategies can provide satisfactory management of individual conditions. The protocol for the management of TCS can be divided into three epochs. From birth to age 2, airway and feeding problems are the main focus. From age 2 years to 12 years, speech therapy and reconstruction of the upper face is performed either with bone grafts or with vascularized bone flaps. From age 13 years to 18 years, orthognathic surgery with further revision or bone grafting should be performed.⁹ Proposed protocol for the staged reconstruction is (1) upper facial reconstruction with specially designed outer calvarial table, (2) mandibular lengthening by distraction osteogenesis and orthognathic surgery to correct the birdlike facial appearance and anterior open bite after distraction, and (3) lipofilling for the correction of residual depressive deformities. Apart from a multistage surgical treatment, a combined multidisciplinary approach is required, mainly due to hearing impairment and occlusal disturbances.

Bilateral mandibular lengthening by gradual distraction can safely and effectively elongate the mandible and the surrounding soft tissues. Resultant open bite can be closed with subapical osteotomy, while the chin projection can be improved by advancement genioplasty. Bony reconstruction of the zygoma or the periorbital, if required, should be undertaken. Pedicled bone flap for the reconstruction of the orbit and zygomatic complex in young patients as a free bone graft has the tendency of bone resorption and multiple onlay bone graft may be added in the later stage. However, for adult patients, the reconstructed bone framework using the outer cranial table can well maintain the bony facial contour of the orbital zygomatic region. The residual depressive deformities in the temporal and cheek regions can be treated with lipofilling. Primary midface augmentation with free vascularized tissue can be used as a safe, effective and reliable procedure to restore the form and function. Composite tissue allotransplantation (CTA) offers an intact vascularized bone that can be reshaped for the reconstruction of the nose, lips and eyelids with correct donor match.

For the most severe form of the disease with dyspnea and paroxysmal apnea, the treatment aim should be at improving the respiratory function by restoring the patency of the nostrils and the distraction of the mandible. Eyelid correction can be done using a musculocutaneous flap transposition from the upper eyelid (Z-plasty). The zygomatic bone and the lateral wall of the orbit can be reconstructed by iliac bone grafts. The auricular reconstruction by means of a modified Brent method can be done bilaterally. Ear defects in these patients necessitate the replacement of the existing anatomic residuals of the ears with custom-made prostheses involving a computer-aided design/computer-aided manufacturing for manufacturing ear prostheses and using innovative prototyping technologies together with laser scanning of the defective regions of a patient's face, 3D anatomic models from an ear digital library and rapid prototyping of both substructures for bar anchoring and molds for silicone processing.¹⁰

Even after multiple surgeries, there still exist some deficiencies in restoring the form and function. Better techniques for regeneration and tissue engineering may minimize the devastating consequences of the orofacial birth defects.

CONCLUSION

Treacher Collins syndrome presents with a plethora of abnormal clinical features. Diagnostic imaging provides precise information about the abnormal variations in the facial skeleton and helps to differentiate between the various craniofacial syndromes. Such patients when diagnosed should be subjected to surgery for correction of both esthetics and function to avoid further psychosocial trauma.

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