

# Treacher Collins Syndrome

Ambarkova Vesna\*

*Department of Pediatric and Preventive Dentistry, Faculty of Dental Medicine, St. Cyril and Methodius University, Skopje, Republic of Macedonia.*

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Treacher Collins syndrome (TCS) is a genetic disease that alters the development of bones and other tissues in the face, and presents variable expressivity. At least three genes *TCOF1*, *POLRID*, and *POLRIC* were recognized to be at the origin of this syndrome which may be inherited through either an autosomal dominant or autosomal recessive pattern. TCS changes can be divided into otological, ophthalmic and dental malformations. Dental abnormalities occur in 60% of cases and may appear as tooth agenesis, enamel opacities, widely-spaced teeth, skeletal open bite, distalization of the mandible, bird profile, ectopic eruption of maxillary first molars, improper positioning of the teeth and jaw, and hypoplasia of the mandible jaw. Receding chin and other changes in face structure can be corrected by plastic surgery. As multiple body systems are affected in TCS, long-term follow-up care and the collaboration of a multidisciplinary team care is necessary in order to achieve better physical and psychosocial performances.

**Keywords:** Treacher Collins syndrome, craniofacial defects, treatment, genetic

Treacher Collins syndrome (TCS) is a genetic disease that causes skull bones development defects and alters other tissues in the face. This syndrome shows variable expressivity from almost unnoticeable face changes to severe facial and ear malformations, cleft palate and restricted airway. The syndrome is named after Edward Treacher Collins, an English surgeon and ophthalmologist who described its essential features in 1900, although it was previously described by Thomson and Toynbee in 1846. Later, during the 1940s, extensive reviews of the disorder were published by Franceschetti and his colleague who used the term mandibulofacial dysostosis (1). TCS occurs with an incidence of 1 in 50 000 live births (2). It is noteworthy that eponyms usage in the head and neck diseases is found mainly when medically compromised individuals are encountered (3).

Treatment and management of disabled children with TCS is a great challenge not only in the medical field, but also among the dental professionals. Various articles, in the dental and medical literature described the etiology, clinical features and treatment protocols (4- 9).

## **Etiology and genetic aspects**

TCS probably derives from inhibition of the facial structures corresponding to the first and second branchial arches (9). Although both autosomal dominant and autosomal recessive inheritance pattern have been described for this syndrome, but most of the time other members of the family do not seem to be affected. The responsible gene was first mapped to the long arm of chromosome 5 (5q32-q33.1) (7) which is the locus of *TCOF1* named after Treacher Collins and Franceschetti, and which encodes for a treacle

\*Correspondence: Department of Pediatric and Preventive Dentistry, Faculty of Dental Medicine, St. Cyril and Methodius University, Skopje, Republic of Macedonia. E-mail: vesna.ambarkova@gmail.com

ribosome biogenesis factor 1. Mutations in *TCOF1* and RNA polymerase I subunit D (*POLR1D*) located on 13q12.2 cause the autosomal dominant form of Treacher Collins, and mutations in RNA polymerase I subunit C (*POLR1C*) located on 6p21.1 cause the autosomal recessive form (10).

When an affected child is born, it is recommended to perform genetic analyzes both in the child and parents. This will help to recognize the gene involved in disease development in the family and to determine the pattern of inheritance. Relatively, genetic counselling can be offered to parents. Also, the parents could be affected and show a mild form of the disease that has remained undiagnosed.

### Diagnosis and prevention

The diagnosis of TCS relies on clinical and radiographic examinations. Mutations in the main genes responsible for TCS can be detected after chorionic villus sampling or amniocentesis, but prenatal diagnosis cannot be always guaranteed as all genes involved in disease development are not yet known. Ultrasonography can be used during the second and third trimesters of pregnancy to detect severe craniofacial abnormalities, but milder cases may remain undiagnosed. *TCOF1* protein plays a key role in pre-ribosomal processing and ribosomal biogenesis (11). De Peratta et al. found a positive correlation between the expression of *CNBP* (cellular nucleic acid-binding protein also known as zinc finger protein 9) and *TCOF1* in mesenchymal cells of TCS subjects as well as normal individuals. Accordingly, they suggested the use of *CNBP* as a target for new alternative therapeutic treatments in order to reduce craniofacial abnormalities in TCS as well as other neurocristopathies (12).

Deficient ribosome biogenesis which occurs in TCS is insufficient to meet the proliferation and growth needs of cells during embryonic development. It is assumed that the changes occur from 19<sup>th</sup>-28<sup>th</sup> days of intrauterine development due to destruction of the trigeminal neuron cells (of unknown origin) and generalized lack of

mesenchymal tissue, leading to underdevelopment of the upper and lower jaws. Because TCS is highly variable, it is generally assumed that other genetic and possibly environmental factors may also play a role in the variable expressivity of the disease (11). Genetic counseling is highly recommended for affected individuals and their families for prevention of further affected child birth.

### Clinical Aspects

TCS changes can be divided into three groups: otological, ophthalmic and dental modifications. Otological abnormalities can be mild to severe conductive hearing loss due to middle ear structures malformations; small or absent external ears; deformities of the external ears (hypoplasia or low position of the ear shells, presence of skin extensions and blind fistula in the area before the ear shells), absence of the outer ear canal (atresia), stenosis of the external auditory canal, and often deafness.

A child with TCS may have sleep apnea (13, 14), conductive hearing loss, which may necessitate the use of hearing aids. Some individuals can be affected severally, and they may develop life-threatening breathing problems known as infantile apnea. Ophthalmic findings associated with TCS include antimongoloid palpebral position, narrowed tear ducts (dacryostenosis), notching (coloboma) of the lower eyelid, downward angle of the upper and lower eyelids (downward slanting palpebral fissures), partial or complete absence of the lower eyelashes in the inner corner of the eye, drooping eyelids, vision loss.

Dental abnormalities appear among 60% of individuals with TCS. Missing teeth (tooth agenesis), discoloration of the teeth (enamel opacities), widely-spaced teeth, skeletal open bite, bite distal (distalization of the mandible), "profile of a bird", abnormal eruption of certain teeth (ectopic eruption of maxillary first molars) and malocclusion (improper positioning of the teeth and jaw) and hypoplasia of the mandible jaw with a unique concavity on the lower edge of the mandible, which can be seen well in cephalometric radiograph, are

among dental malformations observed in TCS. TCS is most often characterized by short posterior vertical height and an anterior open bite. Less frequent findings associated with TCS are congenital heart defect, abnormal scalp hair pattern (front of the ears and extending toward the cheeks), an abnormally wide mouth (macrosomia occur in 15% of cases), notching of the upper eyelid, hypoplasia or absence of zygomatic bones, widely spaced eyes, nasal deformity, cleft palate and highly arched roof of the mouth (high Gothic palate accompanied by a cleft palate in 30% of cases).

### Treatment

There is no cure for TCS, and treatment is conducted in accordance with the special needs of each patient. The introduction of stem cells for improving the surgical outcome might be an option for treating craniofacial abnormalities. Although stem cells has enormous potential in engineering tissues like bone and cartilage, however, *in utero* correction of prenatally diagnosed craniofacial anomalies may have high mortality risk for mother and fetus (2).

When TCS affected small infants are scheduled for mandibular surgery under general endotracheal anesthesia, the fiberoptic intubation method through a laryngeal mask airway, described by Ellis et al. can be successfully used (4, 51). This method was also used in a 12-year old boy, where concomitant nasal fiberoptic intubation and oral mask ventilation were performed, in order to place a nasal endotracheal tube, but at the expense of prolonged respiratory depression in the patient. Therefore, simultaneous fiberoptic nasal intubation and mask ventilation may help the substitution of the laryngeal mask airway usually used in cases of inadequate ventilation by the endotracheal tube (16).

Hearing loss treatment can ensure better performance in school. The children with TCS have to be followed by a plastic surgeon, because they may need a series of operations to correct birth defects. Receding chin and other changes in face structure can be corrected by plastic surgery (17-19).

Da Silva Dalben et al. investigated the oral health status of 15 individuals with TCS. They did not find an association between the gingival index and the presence of mouth breathing, but found predominance of D component in both the dmft and DMFT indexes. The need for dental care for TCS patients was indicated by a need for restorative dental treatment in 60% of the patients (20). Typically, a high incidence of dental caries is observed in TCS patients. Unfortunately, even simple dental restorative procedures can be challenging in these patients due to the presence of other medical complications such as congenital heart defects, decreased oropharyngeal airways, hearing loss and anxiety toward treatment (21). Evaluation of the morphology of interforaminal region by cone-beam computed tomography showed no statistically significant difference between normal subjects and patients affected by TCS (22).

The Orthodontic treatment focuses on the expansion of the upper jaw with mobile devices. If the cleft palate is present, the design of the orthodontic appliance is specially adapted. In the presence of the permanent dentition, the application of fixed orthodontic appliance is indicated in order to establish satisfactory intercuspation and establish proper leveling of the jaws arches. Angle Class II skeletal relationship of the jaws is retained because of the underdevelopment of the lower jaw (23).

A retrospective review of all Treacher Collins patients from 1993 to 2007 performed by Nguyen et al. in Toronto showed that the combined orthodontic-orthognathic approach is often necessary for the correction of the malocclusion. They concluded that bimaxillary orthognathic surgery gives long-term dental and skeletal stability in TCS patients (24). Brevi et al. described mandibular distraction as an adequate surgical treatment in severe hypoplastic cases, when gonial angle control is necessary. In that case bidirectional or multidirectional devices have an advantage over intraoral devices. Mandibular distraction represents an alternative to tracheostomy (25). Okada et al.

demonstrated an orthodontic approach for a patient with TCS. After eruption of permanent teeth, they applied a multibracket fixed appliance for alignment of the teeth and bite closing. After 4 years and 6 months of active treatment, they used Hawley retainers for stabilization (8).

Heller et al. proposed a novel procedure of genioplasty distraction and hyoid advancement to optimize epiglottal positioning. This technique is effective for solving problems with obstructive sleep apnea in TCS patients (26). When planning the reconstructive options for patients with TCS, surgeons must consider the complex interplay between craniofacial growth and the possible effects of early surgery on future growth (27). A staged reconstruction protocol was proposed by Zhang Z et al. consisting of “[1] upper-facial reconstruction with specially designed outer calvarial table, [2] mandibular lengthening by distraction osteogenesis technique 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” (28).

## Conclusion

Because TCS affects several body systems, experienced, multidisciplinary team care is necessary in order to achieve better physical and psychosocial performances. Also, important achievements regarding surgical repair, airway management, feeding and breathing support, orthodontic needs, and speech language therapeutic follow-up are needed (29). Moreover, vision and hearing problems management and long-term follow-up care are recommended. Oro-facial team including pediatric otolaryngologist, audiologist, plastic surgeon, geneticist, psychologist, dental surgeons, and other healthcare professionals should be involved in TCS management. Further cellular and molecular investigations, mouse genetics studies, and experimental embryology should provide new insights into the molecular pathogenesis of TCS.

## Conflict of interest

The authors declared no conflict of interest.

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