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## Treacher Collins syndrome- a case report and review of literature.

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### Abstract

Treacher Collins syndrome (TCS) or Franceschetti syndrome is an autosomal dominant disorder of craniofacial development with variable expressivity. It is named after E Treacher Collins who described the essential components of the condition in 1900. Incidence of this syndrome is approximately 1 in 50,000 live births and it affects both genders equally. It affects structures which are derivatives of the first and second brachial arches. The most common manifestations of TCS are the antimongloid slanting of the palpebral fissures, colobomas of the lower eyelid, hypoplasia of zygoma and mandible; and a variety of ear abnormalities. This article describes clinical and radiographic features of TCS in an 18 yr old female who had reported to the department of Oral Medicine and Radiology with the complaint of forwardly placed upper anterior teeth. Also pathogenesis, prenatal diagnosis, differential diagnosis, management and preventive aspects are discussed.

**Key words:** *Hypoplasia, mandible, palpebral fissures, Treacher-Collins syndrome, zygoma.*

**Introduction**

Treacher Collins syndrome is a severe congenital disorder of craniofacial development characterized by numerous developmental anomalies that are restricted to the head and face. Hypoplasia of the facial bones, particularly the mandible and zygomatic complex, is an extremely common feature of TCS. Although the condition was probably first described by Thomson (1846) followed by Toynbee (1847) and Berry (1889), it is named after E Treacher Collins who described the essential components of the syndrome in 1900. The first extensive review of the condition was done by Franceschetti and Klein in 1949, who coined the term mandibulofacial dysostosis to describe the clinical features (1). In England and on the American continent this abnormality is described as the “Treacher Collins syndrome” and on the European Continent as “Mandibulo-facial dysostosis” or “Franceschetti syndrome” (2). *With patient’s consent, clinical and radiographic features of TCS in an 18 yr old female are described in this article.*

**Case Report**

An 18 yr old female reported to the Dept. of Oral Medicine and Radiology with the chief complaint of forwardly placed upper anterior teeth. Family history revealed that her father and grandmother had typical signs of the Treacher Collins Syndrome. On extra oral examination, she presented with antimongloid slanting of the palpebral fissures with sparse eyelashes on the lower eyelid. There was hypoplasia of the malar prominence (Figure 1). Micrognathia was also evident. The maxilla appeared to be prognathic. Thus face had ‘bird like’ appearance.



*Fig. 1. Front view of patient showing hypoplasia of facial bones, down sloping palpebral fissures, with scanty lower eye lashes.*

Intraoral examination revealed narrow high arched palate. The maxillary incisors were proclined and there was spacing in the maxillary and mandibular anterior teeth. There were root stumps in place of 26, 36 and 46. Radiographs revealed prominent antgonial notch, short ramus (Figure 2), hypoplasia of the mandible, proclined upper



*Fig. 2. OPG showing prominent antgonial notch, short ramus.*



**Fig. 3.** Lateral cephalogram showing hypoplastic mandible, prominent nose and proclined upper anteriors.



**Fig. 4.** PA Water's showing hypoplasia of zygomatic bone and maxillary sinus.

anterior teeth, steep occlusal plane (Figure 3), hypoplasia of zygomatic bone and maxillary sinus (Figure 4). Correlating clinical and radiographic findings a diagnosis of TCS was made.

Treatment plan comprised of extraction of root stumps of 26, 36 and 46. As patient's main concern was esthetics, the patient was explained regarding the need for pre-surgical orthodontic treatment for leveling and aligning and closure of spaces followed by orthognathic surgery that would require *Le Fort I* osteotomy for superior and backward positioning of the maxilla and bilateral sagittal split osteotomy for mandibular advancement along with genioplasty. Also genetic counseling was provided to the patient.

## Discussion

Treacher Collins syndrome or Franceschetti syndrome is an autosomal dominant disorder of craniofacial development which has an incidence of approximately 1 in 50,000 live births (3). It affects both genders equally. While 40% of cases have a previous family history, the remaining 60% appear to arise as a result of a de novo mutation (4). In our case, patient had family history of the syndrome.

Several hypotheses were proposed to explain the pathogenesis of TCS including abnormal patterns of neural crest cell migration, abnormal domains of cell death, improper cellular differentiation during development or an abnormality of the extracellular matrix. *Mann and Kilner* assumed the etiology to be an inhibitory process occurring towards the seventh week of the embryonic

life and affecting the facial bones deriving from the first visceral arch. *John Mckenzie* suggested that the cause of the abnormality is a defect of the stapelial artery which causes maldevelopment in its own field of as well as in the region of the first visceral arch (5). Recently genetic, physical and transcript mapping techniques have identified the gene mutated in TCS which is designated as TCOF1 and mapped to human chromosome 5q32–33.2 locus. It was found to encode a low complexity, serine/alanine-rich, nucleolar phosphoprotein termed Treacle (6). *Valdez et al.*(7) suggested that haploinsufficiency of treacle in TCS patients might cause insufficient rRNA production in the pre-fusion neural folds, resulting in abnormal craniofacial development. (The cephalic neural crest cells probably require a higher threshold concentration of rRNA for their survival and proper differentiation during early embryogenesis).

The structures affected in TCS are derived from the first and second pharyngeal arch, groove and pouch (8). *Franceschetti and Klein* (1949) (9) reviewed the literature and described the typical characteristics of the syndrome as follows: 1) Antimongoloid palpebral fissures with either a notch or coloboma of the outer third of the lower lid, and occasional absence or paucity of the lashes of the lower lid. 2) Hypoplasia of the facial bones, especially the malar bones and mandible. 3) Malformation of the external ear, and occasionally of the middle and inner ear, with low implantation of the auricle. 4) Macrostomia, high palate, malocclusion and abnormal position of the teeth. 5) Atypical hair growth in the form of tongue-shaped processes of the hair-line extending

towards the cheeks in the pre-auricular region. 6) Association at times with other anomalies, such as obliteration of the naso-frontal angle, pits or clefts between the mouth and ear, and skeletal deformities.

After this description was published, some of these features were regarded as being of lesser importance and some were emphasized in the diagnosis. Thus Axelsson et al (1963) (9) named the following features as “obligatory”: 1) Antimongoloid palpebral fissures. 2) Anomaly of the lower lid: coloboma of the outer third, or deficient lashes, or both. 3) Hypoplasia of the malar bones. 4) Hypoplasia of the mandible. In our case, all obligatory features were present.

*Mittman (10) described additional features of scarring alopecia and acne keloidalis nuchae in a patient who had some of the classic features of TC S. Hertle R (8) described ocular findings in 24 patients with TCS. All patients had some eye abnormality like amblyopia, anisometropia, refractive errors, strabismus, lid and adnexal abnormalities and vision loss.*

*Franceschetti and Klein (8) described five clinical forms: (1) the complete form (having all known features), (2) the incomplete form (presenting variably with less severe ear, eye, zygoma, and mandibular abnormalities), (3) the abortive form (only the lower lid pseudocoloboma and zygoma hypoplasia are present), (4) the unilateral form, (anomalies limited to one side of the face), and (5) the atypical form (combined with other abnormalities not usually part of the typical syndrome). In our case, patient presented incomplete form of syndrome.*

It is characterized by bilateral and symmetrical malformations. The penetrance is considered to be complete, but there is a high inter and intra-familial phenotypic variation, ranging from cases with perinatal death due to airway obstruction by severe orofacial malformations to those that are not clinically diagnosed (11).

Prenatal diagnosis of TCS has only been performed in families with a history of TCOF1 using either fetoscopy or ultrasound imaging in the second trimester of pregnancy (approximately 18 weeks) when termination of pregnancy is psychologically a traumatic procedure. However, the onset of TCS abnormalities occurs very early during human embryonic development, typically within the first 4–8 weeks. Hence first trimester prenatal diagnosis would seem to be preferable, particularly if the family feel that termination of pregnancy is desirable in the event that the fetus is affected (1). Phenotypic diagnosis at this stage (first trimester) even with the most sophisticated ultrasonography available today is not possible. Although linkage analysis (molecular analysis) has been used to make first trimester diagnostic predictions in a pregnancy at high risk of producing an affected child, it is not possible to predict how severely affected a fetus might be using this approach alone; consequently, ultrasonography is an invaluable aid to prenatal diagnosis, as

this technique may provide information about the severity of affected pregnancies and can be used to evaluate fetal progression (12).

Nager and Miller syndrome should be included in the differential diagnosis of TCS. Nager syndrome has similar facial features to TCS, particularly in the region of the eyes (downward slanting with a deficiency of eyelashes). However; the mandible is usually more hypoplastic, the lower lid colobomas are rare, and preaxial limb abnormalities (hypoplastic, or aplastic thumbs, fused radius and ulna) are a consistent feature of Nager syndrome, unlike TCS (13).

Miller syndrome also has some similarity in the facial features to TCS, in addition it has postaxial limb defects (absence or incomplete development of the fifth digital ray of all four limbs) and ectropion or outturning of the lower lids (5). Also cleft lip, with or without cleft palate, is more common than in TCS and some patients may exhibit congenital heart defects.

*Management of individuals affected by TCS requires a multidisciplinary approach involving craniofacial surgeons, orthodontists, ophthalmologists, otolaryngologists and speech pathologists. Depending on the clinical manifestations and severity, management may require tracheostomy at birth, multiple surgeries to correct eyelid coloboma and cleft palate (in the early years) followed by orbital reconstruction and maxillo-mandibular osteotomies (at about 5–7 years of age) (6).* The development of speech and language skills depends on the child’s ability to hear during the first 3 years of life. As the great majority of these patients are of normal intelligence, early recognition of deafness and its correction with hearing aids or surgery, when possible, is of great importance for development. An affected parent of either sex will transmit the defect to 50% of his or her offspring in accordance with mendelian laws of genetics. This emphasizes the importance of genetic counseling to affected individuals (10).

In animal models it is shown that chemical and genetic inhibition of p53 function can repress the wave of neuroepithelial apoptosis associated with TCS and in doing so prevents the pathogenesis of craniofacial anomalies. However, p53 performs many critically important cellular functions and suppressing p53 function completely is a very risky approach given that loss-of-function mutations in p53 are the most common mutations associated with cancer and tumorigenesis. Therefore appropriate titration of p53 function is key in preventing the pathogenesis of TCS without risking the onset of tumorigenesis (6).

## Conclusion

Individuals with severe form of TCS usually undergo, over a period of time, multiple major reconstructive surgeries that are rarely fully corrective and stem cell

therapy is unlikely to benefit the reconstructive repair of severe craniofacial malformations. Consequently, more research should be directed on preventive aspects of this syndrome.

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