Treacher Collins Syndrome – Case Report and Review

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Abstract

Treacher collins syndrome is a rare, genetic disorder associated only with craniofacial abnormalities. It is frequently inherited in an autosomal dominant pattern. Clinical diagnosis can be made based on a combination of anti-mongloid palpebral fissures, hypoplastic facial bones, ear abnormalities, cleft palate, with normal intelligence. This paper describes a 13 year old patient suspected with Treacher Collins syndrome. He displayed a severe form and a classic phenotype, demonstrating all cardinal features of the disorder. Along with CBCT data explaining changes in mandibular parameters, this paper also reviews the syndrome in the light of recent publications with emphasis on pathogenesis (role of neural crest cells) and broad discussion on the syndrome perse.

Key Words: Treacher Collins syndrome, Mandibulofacial dysostosis, Mandibular hypoplasia, Autosomal dominant syndrome, Neural crest

Introduction

Treacher Collins syndrome (TCS) also referred as mandibulo-facial dysostosis is a rare genetic disorder with an approximate incidence of 1 in 50000 live births. It is inherited in 40% cases and occurs as a fresh mutation in 60% cases. It is typically characterized by abnormalities in the first and the second branchial arches, with no racial or gender predilection. TCS is associated with a mutation in either of the 3 genes: TCOF1, POLR1C or POLR1D [1]. Common manifestation include hypoplasia of facial bones particularly mandible, zygoma and maxilla, anti-mongloid slanting of palpebral tissues, cleft palate, malformation of the external ear with conductive deafness and coloboma of the lower eyelid [1]. Here in, we report a patient suspected with TCS from our departmental archives to discuss on the syndrome.

Case Presentation

Patient was 13 years old and his complaint was unsatisfactory facial growth and forwardly placed upper front teeth. Family history revealed an absence of consanguineous marriage and all his three siblings were normal.

Figure 1. *A severely affected patient with treacher collins syndrome. Anti-mongoloid slant of palpebrae, strabismus, absence of eyelashes on lower lid and coloboma.*

No such signs were observed in the previous 3-4 generations. On physical examination patient's palpebral fissures showed remarkable downward obliquity (anti-mongoloid slants); lower eyelashes were partially absent. Temporo-parietal flattening was evident. Hypoplasia of mandible, protruding upper dentition, and zygomatic and malar hypoplasia gave a narrow facial dimension and bird like appearance to the face (*Figure 1*).

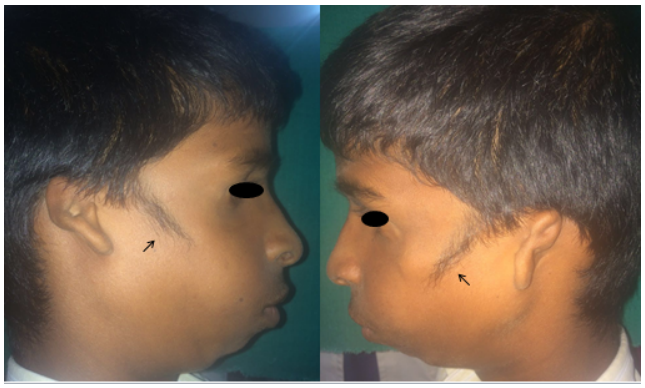

Figure 2. *The presence of hair growing towards cheek, malformed ears and retruded chin.*

The external ears were severely malformed, and hearing loss is partial (conductive type). A classic hair growth pattern was noticed towards the cheek region on both sides (*Figure 2*).

OPG and lateral cephalogram revealed hypoplasia of mandible, upper anterior teeth protrusion and prominent anti-mongloid notch (*Figure 3*). We also advised cone beam computed tomography (13 x 15 cm) to access the craniofacial deformity. Zygoma defect was bilateral, and was classified as a minor type 1 defect (orange arrows in *Figure 4*).

Significant changes were observed in mandibular parameters: antegonial notching, and elevated ramus-body angle and short ramus (*Figure 4*). In crosssectional views, there was temporo-parietal flattening on left side, dipping on right side and loss of glenoid fossa architecture and small condyle on both sides (*Figure 5*).

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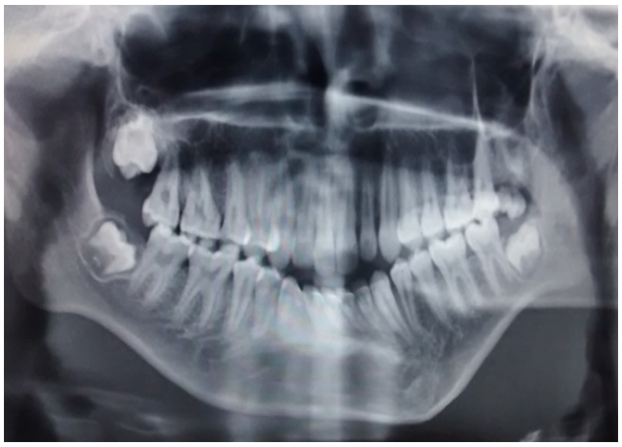

Figure 3. *OPG showing deep mandibular antegonial notch and uneven lower border.*

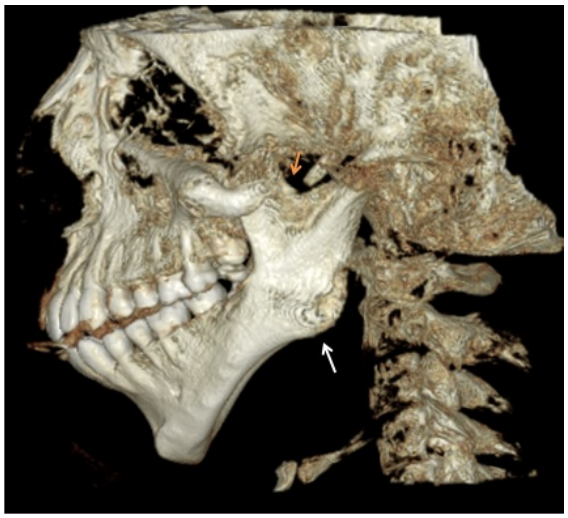

Figure 4. *13 x 15 cm volume reconstructed CBCT shows elevated ramus body angle (white arrow) and mandibular plane angle, shortened ramus, protruding maxillary teeth and partially developed zygoma (orange arrow).*

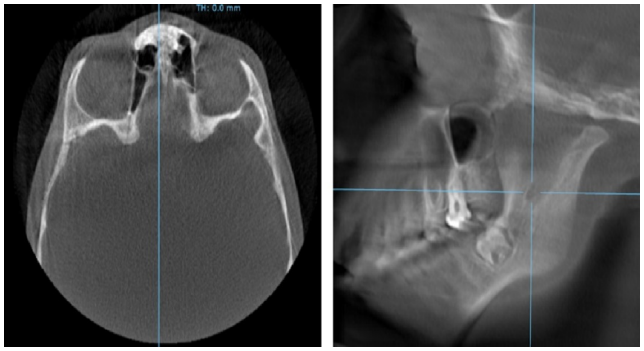

Figure 5. *In cross section there is temporo-parietal flattening (right side) and dipping (left side), deranged glenoid fossa architecture and small condyle on both sides.*

Based on clinical presentation and radiological features, a spot diagnosis of 'Treacher Collins syndrome' was considered. Since family history was negative, the cause could be a denovo mutation involving one of the candidate genes of TCS. This patient is currently undergoing orthodontic treatment for correction of skeletal abnormality using head gear, to compensate maxilla with underdeveloped mandible.

Discussion

TCS is a mendalian disorder which favors an autosomal dominant pattern of inheritance; rarely however an autosomal recessive pattern does occur. In a majority of cases it is caused by deletions or insertions in TCOF 1, but a small fraction are associated with mutations in POLR1C and POLR1D genes (recently identified candidate genes) [1]. Hypoplasia of structures derived from the 1st and 2nd branchial arches is a hallmark feature [2]. This syndrome is primarily a neural crest (NC) defect. NC cells contribute to a majority of face and display stem cell features, capable of differentiating into many cell types: neurons, muscle cells, bone, cartilage etc. During embryogenesis neural crest cells undergo continuous cell divisions and differentiate. As a consequence of continuous metabolic activities they are under heavy oxidative stress.

Neural crest cells are sensitive to the levels of 'Treacle', protein product of the 'TCOF1' gene and also 'polymerase subunit components' coded by POLR1C and D genes. These three genes are necessary for proper ribosome formation and low concentrations impair ribosomal RNA formation that make up RNA subunits. Low ribosome formation triggers p53 mediated apoptotic mechanisms within neural crest cell population [1,3]. Hence TCS is considered as both a neurocristopathy and ribosominopathy [3,4]. Recently treacle was also shown as an interacting partner of proteins that participate in DNA damage response in oxidative stress. The migration of neural crest cells is another cellular event hampered in TCS. The 'Lish domain' of treacle protein is known to contribute to the dynamics of microtubule formation, necessary for NC cell migration. TCS is therefore a result of apoptosis, lack of proliferation and cell migration of neural crest cells. Clinically TCS phenotype exhibits a wide spectrum of features ranging from perinatal airway obstruction leading to death, to mild features. Reasons explaining such wide variation in phenotypes has not yet been characterized.

As with our patient deficiency in structures derived from the 1st and 2nd brachial arch is a classical presentation of TCS and key oral features include the hypoplasia of mandible and maxilla, significant malocclusion and open bite [5]. Dental anomalies are more common but underestimated and underreported. Features like tooth agenesis mandibular premolars (>30% cases), enamel opacites, rotated teeth, ectopic eruption and cleft palate are well documented in these patients [6]. Cleft palate was however absent in our patient. Deformity is usually bilaterally symmetrical, but it happened to be more severe on the left side as revealed in the profile pic and orthopantomogram (uneven borders and severe antegonial notch) (*Figure 3*). Nearly 40% of cases have a positive family history whereas 60% are sporadic cases due to a *denovo* mutation. We believe that our patient developed sporadically, but not from a consanguineous marriage, as with many reported cases. The chances of a similar phenotype in the next generation are 50%, irrespective of the gender.

Diagnostic criteria of TCS according to Franceschetti and Klein: i) Antimongoloid slant of palpebrae with coloboma; ii) Hypoplasia of facial bones (mainly malar bones and mandible); iii) Malformation of the external ear; iv) Dental features such as malocclusion, high arch palate, and abnormal position of teeth; v) Hair growth extending towards the cheek in the pre-auricular region (*Figure 1*). These criteria were filtered by Axelsson who listed main obligatory features; a few investigators later included ocular findings in the criteria. Ocular findings are commonly seen in these patients include strabismus, vision problems and refractive errors, lid and adnexal abnormalities.

In a study by Steinbacher DM and Bartlett SP the ramus-body angle was elevated to 150.28 degrees as opposed to 114.2 degree in controls [7]. The mandibular plane angle was also significantly elevated in these patients. Elevated antigonial angle and deep notch are indicators of reduced mandibular growth and vertical growth pattern. Even condyles show significant reduction in volume [8]. Zygoma is not fully developed and classified into 3 types: minor form (type 1); moderate (type 2); severe (type 3) [2]. The present case fitted the minor form (type 1) showing partial presence of zygomatic complex. Each and every case of TCS is different and treated should be based on structures involved and degree of involvement. 3D modalities such as CBCT can serve as an indispensible tool to assess craniofacial deformity.

Speech problems may also occur with TCS patients. In one study the speech composite score correlated well with TCS severity scores, and 13 of 19 patients had speech deviations [9]. Patients mainly used less commonly intelligible words common with control population and speech and language services may be necessary for TCS patients. This was relevant to our case, as he developed mild speech and communication deficit. Low self esteem and poor socialization were other important concerns with our patient. Facial malformation can have a serious psychological impact on these children. Therefore, it is important to give more attention to such dimensions. Although the deformity can be improved by repeated surgeries there is no cure as such. A multidisciplinary approach is required combining efforts of oral surgeons and orthodontists, paediatricians, audiologists, ophthalmologists and plastic surgeons. TCS patients lead a poor overall quality of life [10] and can be exposed to healing techniques like meditation to improve psychological distress, outlook and personality.

Nager and Miller syndrome are two related syndromes to TCS. Nager syndrome also referred as pre-axial acrofacial dysostosis mimicks treacher Collins syndrome with classic combination of mandibular and thumb hypoplasia. These patients have early respiratory problems, micrognathia, normal IQ, speech delays and language problems [11]. Patients with Nager syndrome (NS) may show progressive hearing loss so a careful follow up is essential in case of patients where diagnosis is difficult [12]. Screening for cardiac problems is also important in NS patients.

Although TCS is not preventable, some reports have pointed at a hope for a preventive strategy. In experimental models the compound 'Pifithrin' demonstrated a surprising capacity to inhibit the development of TCS phenotype in mouse models, but there was inadvertent tumor formation. This is risky, but an important link for future studies.

Conclusion

Management of TCS should consist a multidisciplinary approach enabling the patient to attain functionality, aesthetics and improved confidence [13]. New genetic studies and the area of prevention can be a targeted for future research. It is our responsibility to identify this craniofacial disorder, to provide appropriate maxillofacial and orthodontic care, referrals to a geneticist for counselling, to ENT, ophthalmology and plastic surgery departments for possible treatment. Little is known about alternative genes in TCS.

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