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Treacher Collins Syndrome

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Abstract:
Treacher Collins syndrome (TCS) is a rare genetic disorder characterized primarily by abnormalities in the development of the head and face. Underdevelopment (hypoplasia) of the cheekbones and related structures (zygomatic bones) as well as the jawbone are common findings. Consequently, patients generally have a distinctive facial appearance. The jaws, ears and eyes are commonly affected, potentially causing respiratory, hearing and vision complications. TCS is caused by mutation of the TCOF1, POLR1C or POLR1D genes. In the case of TCOF1 or POLR1D, the mode of inheritance is autosomal dominant, while in the case of POLR1C it is autosomal recessive. Symptoms of TCS are malformed external ears, drooping eyelids, Vision loss and other extremities. Symptoms of TCS related to dental are Missing teeth (toothagenesis), Widely-spaced teeth and Malocclusion. A diagnosis is made based upon a thorough clinical evaluation, a detailed patient history, and identification of characteristic findings. Specialized imaging techniques such as x-rays or computed tomography may be performed to assess the extent of certain craniofacial abnormalities such as middle and inner ear structures. There is no cure for TCS. Treatment is aimed at the specific needs of each individual. Many children require a multidisciplinary approach involving a qualified craniofacial team, which can include a pediatric otolaryngologist, audiologist, pediatric dentist, pediatric nurse, plastic surgeon, geneticist, psychologist and other healthcare professionals. Specific therapies and surgeries depend upon several factors including age, extent or severity of the disorder, overall health and personal preference. Surgery for individuals with TCS is best performed at a craniofacial research center. Surgery may be performed to repair cleft palate, reconstruct or lengthen the jaw or to repair other bones in the skull (e.g., cheekbones, zygomatic complex). Artificial teeth, braces and dental implants may be necessary to treat dental anomalies such as misaligned teeth. Dental surgery may also be required in some cases.

Keywords:
Treacher Collins Syndrome, Orofacial features, Genetic disease, Mutations, Treacle,

INTRODUCTION:

Treacher Collins syndrome (TCS) or mandibulofacial dysostosis (OMIM 154500) is an autosomal dominant disorder with high penetrance and variable expressivity (1). The essential features of this syndrome were described by Treacher Collins in the year 1900 (2), but the first extensive description of the condition was described by Franceschetti and Klein in 1949, who used the term mandibulofacial dysostosis (1). The frequency of TCS is 1 in 50,000 live births (2), and approximately 60% of the autosomal dominant occurrences arise as de novo mutation (3). Genetically, the treacle gene (TCOF1) is mutated. It is found on chromosome 5q31.3-32 and encodes a serine/alanine rich nucleolar phosphoprotein responsible for the craniofacial development (4). Other modes of inheritance such as autosomal recessive transmission and a role for gonadal mosaicism and chromosomal rearrangement in the causation of this syndrome have also been proposed (5). TCS is characterized by downward slanting palpebral fissures and hypoplasia of the zygomatic arches (6). Other craniofacial alterations of the syndrome are mandibular hypoplasia, coloboma, total or partial absence of lower eyelashes, accessory skin tags or blind pits between the tragus and the mandibular angle, external ear malformations, hearing loss, and malformations of the heart, kidneys, vertebral column and extremities. The oral manifestations are characterized by cleft palate, shortened soft palate, malocclusion, anterior open bite, and enamel hypoplasia (7).

CLINICAL FEATURES:

The disorder is characterised by 1. Abnormalities of the pinnae that are frequently associated with atresia of the external auditory canals and an omalies of the middle ear ossicles. As a result bilateral conductive hearing loss is common (8). 2. Hypoplasia of the facial bones, particularly the mandible and zygomatic complex. 3. Antimongoloid slanting of the palpebral fissures with colobomata of the lower eyelids and a paucity of lid lashes medial to the defect. 4. Cleft palate (9, 10). These clinical features are usually bilaterally symmetrical (11). While non-penetrance is rare, (12) diagnosis and subsequent genetic counselling may be very difficult as expression of the gene is extremely variable. Indeed, some patients are so mildly affected that it is difficult to reach a diagnosis. It is therefore important to be able to recognise the minimal diagnostic criteria for the disorder (12, 13). While 40% of cases have a previous family history, the remaining 60% appear to arise as a result of a de novo mutation. This can create an additional complication in providing genetic counselling where the diagnosis in either of an affected child's parents is in doubt. On the other hand, in cases where apparently un- affected parents have produced an affected child, it is very important to be sure that neither parent is, in fact, minimally affected. In this regard the use of craniofacial radiographs, particularly the occipitomental view, which enables visualisation of the zygomatic complex, may on occasion prove to be useful (13).

SCREENING & DIAGNOSIS:

TCS can be detected using prenatal screening ultrasound (14, 15). Usually, it is difficult to get an satisfactory view of facial structures until after 30 weeks. In addition, traditional two-dimentional imaging is limited and may not be sufficient to assess the fetal profile. Three-dimensional sonographic imaging has been shown to detect these subtle features including downslanting palpebral fissures, micrognathia, and low-set ears/microtia (16). Polyhydramnios is seen as well. Once suspected, other testing can be done to confirm the diagnosis. Amniocentesis may be performed to identify the mutation and rule out other facial dysostoses such as Goldenhar or Nager syndromes, which can have similar appearance on ultrasound (17, 18). High-risk families with or without ultrasound findings should be referred for genetic counseling.

AETIOLOGY & GENETICS:

On the basis that the tissues affected in TCOF1 arise during early embryonic development from the first and second branchial arches, clefts, and pouches, it has been proposed that the condition may arise from abnormal neural crest cell migration or anomalies in the extracellular matrix (19, 20). Sulik et al (21, 22) have produced phenocopies of Treacher Collins syndrome and Nager or Miller syndrome in mice via acute maternal exposure to 13-cis-retinoic acid (a vitamin A analogue) at 9-0 to 9-5 days postfertilisation. These studies showed that the craniofacial and limb anomalies resulted from excessive cell death in the proximal aspect of the maxillary and mandibular processes of the first branchial arch and the apical ectodermal ridge of the limb bud. Theories advanced to explain the possible teratogenic mechanisms of vitamin A include its effects on neural crest cell migration and DNA synthesis (23-25). However, the nature of the genetic defect underlying TCOF1 is unknown. The gene mutated in TCOF1 was initially mapped at 5q31-34 (26, 27). Owing to the low informativity of the majority of restriction fragment length polymorphisms and the relative shortage of large families, subsequent linkage studies have concentrated on the use of highly informative short tandem repeat polymorphisms (STRPs). These studies have permitted the refinement of the localisation of TCOF1 to 5q32-33.1 and the establishment of markers closely flanking the disease locus (28, 29). The creation of a combined genetic linkage and radiation hybrid map around TCOF1 has permitted a yeast artificial chromosome contig to be created across the TCOF1 critical region (30). Additional STRPs isolated from these YACs, and cosmids derived from them, have permitted the critical region to be reduced to less than 540 kb. The high density of STRPs surrounding the TCOF1 locus has permitted postnatal diagnostic predictions to be made (12). Ideally, diagnostic predictions of this type should only be undertaken in families showing significant evidence of linkage to markers in this region of the genome or when the possibility of heterogeneity has been further minimised by the study of additional families. However, as the majority of TCOF1 pedigrees are relatively small it would be difficult to detect genetic heterogeneity, should this be a feature of the disorder. In this regard TCOF1 has been associated with a number of different chromosomal anomalies: two apparently balanced translocations, t(6;16)(p21.31;p13.11) (9) and t(5; 13)(qll;pl1), (31) and two interstitial deletions del(4) (p15.32p 14) (32) and del(3) (p23p24. 12), (33) which raise the possibility that the disorder may be heterogeneous. However, in each of these cases linkage analysis with a series of familial cases from well documented TCOF1 families failed to show cosegregation with markers for the relevant region. Moreover, the chromosome 6 translocation did not ultimately completely cosegregate with the disease phenotype, (13) while in the remaining cases the facial gestalt of the patients did not entirely conform to the clinical criteria of TCOF1. Furthermore, while genetic heterogeneity in TCOF1 cannot be excluded, all of the families that have been analysed to date support linkage of the disease locus to the same region of the genome, (26-28, 34-36) with none showing clear evidence of non-linkage. To date prenatal diagnosis has only been performed in families with a history of TCOF1 using either fetoscopy (37) or ultrasound imaging (38, 39).

SURGICAL TREATMENT:

Preoperative planning and assessment should begin as early as possible. A multidisciplinary craniofacial team approach is critical to coordinate oral, ocular, dental, pediatric, and craniofacial care. Patients will require preoperative imaging usually as CT scans for planning, measurement, and implant fabrication. Newer computer-aided design/computer-aided manufacturing (CAD/CAM) technology allows preoperative simulation—either virtually or by model—to assess developing tooth buds, design osteotomies, hardware placement, and tongue position. TCS patients typically will need multiple surgical procedures and staged treatment may continue throughout the patient's childhood and adolescence.

Mandible:

The characteristic microretrognathic TCS mandible is a priority for surgical evaluation as it can be markedly hypoplastic and can lead to glossoptosis and upper airway obstruction. In addition, the pharynx has been noted to be abnormally hypoplastic and narrow (40). Newer techniques allow osteogenesis enable neonatal mandible advancement to relieve airway obstruction (41, 42). Possible downsides to neonatal distraction include difficulties with hardware fixation due to poor bone quality and stock. Also, absence of a functional TMJ and/or an aplastic condyle may preclude distraction and tracheostomy may still be required. Mandibular distraction planning can be challenging because the TCS mandible may be uniplanar without a true mandibular angle. To correct this phenotype, two vectors of distraction must be applied—one to recreate mandibular height (ramus) and one to recreate mandibular length (body) (43). Recent strategies to simplify this process include the use of curvilinear distraction devices (44, 45).

Oral surgery:

Malocclusion is present in nearly all TCS patients. The more severe pathology often shows a steep occlusal plane, an anterior open bite, and irregular dentition. The shortened mandible in combination with normal anterior maxillary height results in a bird-like appearance with a prominent nose and midface with a retruded lower third of the face. Once skeletal maturity is reached, bimaxillary surgery may be performed. LeFort I with bilateral sagittal split osteotomy is usually performed in late adolescence to level the occlusal plane (46). Dentition can also be abnormal with missing, malrotated, or malpositioned teeth (47). Oral hygiene can be problematic and high plaque buildup has been shown to be significant in TCS patient (48). Orthodontics can help establish improved bite and intercuspation. However, extraction and implants may be necessary in some cases as repeated surgical intervention combined with poor bone stock subject the tooth roots to potential devascularization and injury (49).

Palatoplasty:

Cleft palate is a commonly reported finding in TCS and is present in approximately one-third of cases. Once the airway is secure and stable, palatoplasty can be planned. In addition to speech, palate repair is important for feeding, growth, and development. Preferably, palatoplasty is timed as early as the first year of life. However, unlike other cleft palate patients, TCS cleft palates may be more challenging because of a high arch, smaller oropharynx, limited interincisal opening, and thin, atrophic soft tissues. Bresnick et al noted an increased risk for fistula formation in TCS patients compared with other syndromic cleft palate patients after palate repair (50). They propose that the vascularity of the mucoperiosteum in TCS is limited; therefore, minimal flap undermining and elevation should be done when performing palatoplasty in TCS.

Soft tissue reconstruction:

Coloboma of the lower eyelid is preferably corrected according to Tessier method (51), which consists in Z-plasty for cutaneous lengthening, overlapping sutures of the preseptal orbicularis muscle and canthopexy. Preferred method of eyelid repair is the transposition of pedicled upper eyelid skin-muscle flaps to the lower eyelid deficient region (Z-plasty). Simultaneously the lateral canthi correction is performed to normalize the orbital area. Auricular reconstruction is one of the most difficult problems. The low-set auricular remnants, hairy skin and depressed area produce the main difficulties. The methods described by BRENT (52) and NAGATA (53) represent the current standard of autogenous reconstruction.

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. Thus more research should be directed on preventive aspects of this syndrome.

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