Review Article

Treacher Collins syndrome: A comprehensive review on clinical features, diagnosis, and management

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Abstract

Treacher Collins syndrome is a rare genetic disorder that affects the bone development, resulting in significant craniofacial deformities. The syndrome is characterized by cleft palate, micrognathia, low-set or small ears, and sparse eyelashes. These characteristic symptoms guide for the diagnosis. However, the manifestations may resemble other diseases, which makes the clinical diagnosis difficult. Although the majority of cases are clearly diagnosed at birth, genetic counseling and imaging scans, such as x-ray or computed tomography, may help to confirm the diagnosis. The severity of the disease varies among patients, ranging from mild undiagnosed cases to severe marked deformities. Nevertheless, airway difficulty at birth represents a significant challenge for anesthesiologists since these patients have abnormal development of zygomatic arch, which may result in airway complications. Therefore, proper management requires multidisciplinary departments, including pediatrics, neurosurgery, otolaryngology, audiology, plastic surgery, and genetics. Hence, it can be inherited in an autosomal dominant manner; genetic counseling is also needed.

Keywords: Diagnosis, features, multidisciplinary, pediatrics, syndrome, Treacher

Introduction

Treacher Collins syndrome (TCS) is an autosomal dominant disorder of craniofacial morphogenesis with a high degree of penetrance but variable phenotypic expression, which affects approximately 1 in 25,000 to 1 in 50,000 live births, and there is no sex predilection, highlighting the rarity of this syndrome.[1-3] The complete etiology of TCS is not yet fully understood. In about 10% of cases, it remains unknown. This may suggest a role of other genetic mechanisms in the pathogenesis of TCS.

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TCS is also known as mandibulofacial dysostosis and Franceschetti-Zwahlen-Klein syndrome.[3] This syndrome is generally characterized by bilaterally symmetrical abnormalities of tissues within the first and second branchial arches, which are mainly populated by cranial neural crest cells (NCCs).[4,5] Several hypotheses were researched and discovered to explain the cellular basis of this disorder; these theories included abnormal NCC migration, improper cellular differentiation during development, or a defect in the extracellular matrix.[6-8] The most characteristic finding in TCS patients is hypoplasia of the malar bones, with clefting through the arches and partial formation of the residual zygomatic complex.[9] The degree of malformation present at birth is stable and non-progressive with age.[10] More than 60% of TCS cases do not have a previous family history and are thought to arise as the result of a de novo mutation.[11] Spontaneous mutations can occur, and the inherited form and mutations can

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be spliced, nonsense, or deletion variants. All the mutations arise from insertion of a premature termination codon.[3,12] Using genetic, physical, and transcript mapping techniques resulted in the identification of the gene mutated in TCS, designated TCOF1, which was found to encode a low-complexity, serine/alanine-rich, nucleolar phosphoprotein termed Treacle.[13] The syndrome is linked to chromosome 5q31.3- q33.3 deletions in TCOF1 gene.[14,15] Diagnosis can be achieved indirectly by linkage analysis in a family with multiple affected members, with greater than 95% accuracy if relevant DNA markers are informative within the family. For postnatal diagnosis, a blood sample for DNA isolation from an affected member of his or her family is required. A prenatal diagnosis requires a blood sample from family members and a specimen for culture and DNA isolation through amniocentesis or chorionic villous sampling procedure, performed at 16 to 17 weeks or 10 to 11 weeks, respectively.[16] For optimum care and better quality of life, patients with TCS need a specialized multidisciplinary team from birth through adulthood involving a craniofacial team encompassing primary care pediatricians, otolaryngologists, audiologists, ophthalmologists, dentists, orthodontists, speech therapists, psychologists, genetic counselors, and surgeons across orthopedics, plastic surgery, oral maxillofacial, and oculoplastic subspecialties for early evaluation and longitudinal follow-up[17] This syndrome has a variable degree of phenotypic expression; therefore, proper planning, counseling, and surgical techniques are essential for optimizing patient outcomes. In the presented article, we review the genetics and phenotype in TCS and the range of clinical features and dysmorphology observed in this condition. Diagnostic methods and comprehensive management approaches are outlined, which can serve as a roadmap for treatment planning.

Genetics of Treacher Collins syndrome

It has been reported that 40% of TCS cases possess a family history, and the remaining 60% are the result of spontaneous mutations.[18] TCS includes four clinical subtypes and is genetically diverse. These subtypes are as follows: Variations in the TCOF1 gene cause TCS1, POLR1D gene causes TCS2, POLR1C gene causes TCS3, and the POLR1B gene causes a newly discovered TCS4.[18] However, the clinical manifestations of TCS patients and particular gene variations are not known to be related. The TCOF1 gene includes 27 exons as well as newly identified exons 6A and 16A. Treacle, a protein involved in several cellular functions, is encoded by these exons.[19] Mutations in the Treacle (TCOF1) gene, found on chromosome 5q32, are the chief cause of this syndrome.[19] Hence, these mutations are what cause the distinctive facial deformities, impeding the essential growth and differentiation of craniofacial tissues.[19]

Nuclear export and import signals, phosphorylation sites, and a LisH motif are all present in the Treacle.[18] It further facilitates ribosomal DNA gene transcription, aids in the transportation of proteins and ribosomal subunits, and plays a crucial role in ribosome biogenesis.[18] It could also have an impact on neural crest cell apoptosis during embryogenesis. Point mutations, small insertions, and deletions are some examples of pathogenic variants that have been found in the TCOF1 gene, ultimately leading to alterations in the structure or function of the proteins.[20] The TCOF1 gene is known to have been mutable in several different ways, and exons 10, 15, 16, 23, and 24 are among those that are most susceptible to these mutations.[18] In TCS cases, deletions involving 1 to 40 nucleotides are frequently observed, resulting in the truncation of proteins.[18] TCOF1 gross deletions and specific exon deletions have been found. Affected patients have also been reported to have TCOF1 gene insertions and other variations.[18] In patients with TCS, gross deletions of TCOF1 were found with a frequency of 5%.[18] Research revealed that one patient with a clinical diagnosis of TCS had a 3.367kb deletion. This was the first single exon deletion in the TCOF1 gene to be reported, and it impacted exon 3. Another study also revealed a novel TCOF1 exon deletion spanning two to six. This was the first Chinese population report of a newborn with TCS.[18] In TCS patients who did not exhibit the typical TCS phenotype, a novel TCOF1 pathogenic variant, c. 4138_4142del, p.Lys1380GlufsTer12, was also found.[18] Short cranial bases, hypoplastic maxilla, and hypoplastic mandibles were noted in these cases.

Insertions are the next most prevalent pathogenic variants of the TCOF1 gene. The longest insertion, c.484_668ins185bp, was found to be located in exon 5 in twin sisters.[18] Research on TCOF1 in Chinese patients found five novel variants (two nonsense, one missense, and one splicing.[18] A nonsense pathogenic variant (c. 1622G > A) in TCOF1's exon 11 has also been reported.[18] Nonetheless, recent studies further discovered that other genes associated with ribosome biogenesis and ribosomal RNA (rRNA) transcription, besides TCOF1 mutations, are involved in the pathophysiology of TCS. For example, mutations in the POLR1D and POLR1C genes, which encode parts of RNA polymerase I and III, have been linked to the TCS-like phenotypes with craniofacial abnormalities.[20,21] The craniofacial structures' development is hindered by the loss of function mutations in those genes, eventually leading to interference with ribosome biogenesis.[20,21] Moreover, POLR1B, POLR1C, and Eukaryotic Translation Elongation Factor 1 Delta (EFTUD2), genes involved in RNA processing and transcriptional regulation, have also been linked to mutations in them that are distinguished by craniofacial defects and systemic manifestations.[20,22,23] This POLR1B gene's pathogenic variants have the ability to induce p53-dependent apoptosis, resulting in cranial abnormalities.[18] The importance of tightly regulated gene expression during craniofacial development is accentuated by those genes' inclusion in several stages of RNA processing like ribosomal RNA transcription and splicing.[20,22,23] In TCS patients, research found 20 heterozygous pathogenic variants in the genes POLR1C and POLR1D, and three new pathogenic variants in POLR1B were found.[18] Till this day, there is no relationship found between the phenotype and the type of pathogenic variants in patients with TCS.[18] In Figure 1, TCOF1 mutations are described.[24] Recent research has suggested that the interaction between these genes and other potential genetic or environmental modifiers could play a significant role in the manifestation and severity of TCS symptoms.[20,21]

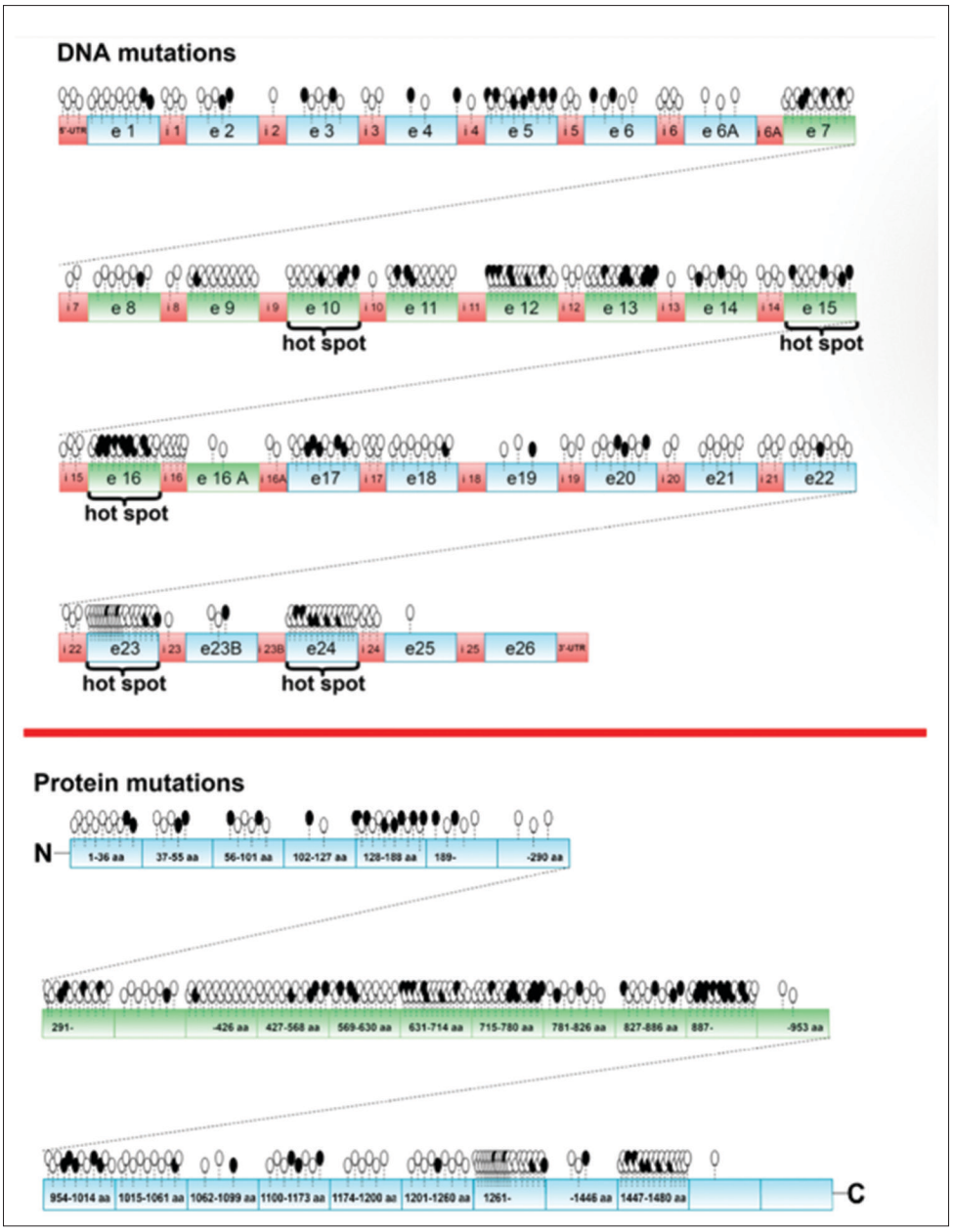

Figure 1: TCOF1 mutations associated with TCS

For instance, variations in the expression levels of modifier genes, epigenetic changes, and environmental factors such as maternal health, nutrition, and exposure to toxins during pregnancy might influence the phenotypic outcomes of TCS. Studies have shown that oxidative stress and hypoxia during pregnancy can exacerbate craniofacial abnormalities in genetically predisposed individuals.[20,21] Additionally, interactions between the primary TCS genes (TCOF1, POLR1C, POLR1D, and POLR1B) and other genes involved in craniofacial development and neural crest cell function might modulate the severity of the syndrome.[18] Developing a better understanding of these interactions may help identify possible treatment targets to lessen the effects of the syndrome and offer deeper insights into the variability of TCS manifestations.

Symptoms of Treacher Collins syndrome

Symptoms of TCS are very variable even in children with the same mutation; thus, clinical detection of the syndrome may be challenging due to the wide variety of features.

Despite this variety, there are certain distinctive facial features that may be used to help the diagnosis of TCS. Micrognathia, hypoplastic zygomatic arches, coloboma of the lower eyelids, external ear anomalies, and downward-slanting palpebral fissures are all frequently associated features.[25,26] The ramifications of these facial abnormalities, such as a small receding chin and sunken cheeks, are caused by the malformation and underdevelopment of several craniofacial structures, including the mandible and maxilla[25] Furthermore, TCS patients

often suffer various degrees of conductive, sensorineural, or mixed hearing loss, often associated with having one or both ears affected[23,26] The outer, middle, and inner ear structural abnormalities are regularly noted.[23] They often have varying degrees of ear deformity, including underdeveloped or absent earlobes. Even though the inner ear does not typically manifest with problems, they frequently have external auditory stenosis or atresia, resulting in varied degrees of conductive hearing loss.[25] One distinguishing feature is the lack of lashes, specifically in the inner third of the lower eyelid. There have been reports of vision loss, congenital cataracts, eye misalignment, and, occasionally, small or nonexistent eyes.[25] Withal, patients with TCS often have underdeveloped soft tissues and facial bones, leading to narrow airways causing trouble breathing.[26] In 46% of cases, TCS patients might also suffer from obstructive sleep apnea, which is caused by underdeveloped cheekbones and jawbones.[25] Anomalies not connected to the craniofacial area have also been linked to TCS. Cardiac defects, limb abnormalities, genitourinary anomalies, intellectual disabilities, cleft palate, and nasal abnormalities are all such examples of these anomalies; however, the occurrence of those systemic manifestations varies.[23,26] The nose, for example, is frequently said to appear hooked; however, several studies have revealed normal measurements, suggesting that the appearance is the result of atrophy in the surrounding tissue.[25] Interestingly, if the child presented with a relatively normal nose and retrognathia, the facial profile usually refereed as birdlike appearance.[27]

Furthermore, problems with the temporomandibular joint could arise, resulting in the patient's immobility and dysfunction. In contrast to TCS, individuals with Goldenhar syndrome, also known as vertebral oculo-auricular dysplasia, have asymmetrical facial anomalies, spinal abnormalities, and epibulbar dermoids.[25] Nevertheless, Nager syndrome shares similarities in facial features with TCS, but it also includes additional characteristics, such as fused radius and ulna bones, and underdeveloped, absent, or duplicated thumbs.[25] Thus, as TCS can have variability of symptoms, it can be classified according to the frequency [Table 1].[18]

The quality of life of TCS patients is greatly impacted by their physical symptoms. Craniofacial abnormalities that cause difficulty breathing, eating, or speaking can cause long-term health problems and necessitate repeated surgeries. The use of hearing aids or other auditory devices, which can be burdensome and stigmatizing, is necessary for people with hearing loss.[23] Emotionally, the clear differences in appearance can cause depression, anxiety, and low self-esteem, especially in social situations where the patients may be the target of bullying or social exclusion. Also, family financial strain and social isolation can result from the need for ongoing medical care and possible learning disabilities that can impede education and career opportunities.[25] Hence, to manage these difficulties, psychological support is frequently necessary. Further, TCS has the potential to affect a person's capacity for social interaction and relationship building. The improvement of the general well-being of people with TCS depends heavily on social support systems and inclusive settings.[25]

Table 1: Frequency of TCS symptoms

Classic Feature	Symptom, Feature	Occurrence in Affected Individuals
Very frequent	Downslanting palpebral fissures	89–100%
	Malar hypoplasia/hypoplasia of zygomatic complex	81–97%
	Conductive hearing loss	83–92%
	Mandibular hypoplasia/micrognathia	78–91%
Frequent	Atresia of external ear canal	68–71%
	Microtia	10–77%
	Coloboma (notching) of the lower lid	54–69%
	Delayed speech development	57–63%
	Asymmetry	52%
	Preauricular hair displacement	24–49%
Rare	Nasogastric tube or gastrostomy in neonates	28%
	Cleft palate	21–33%
	Intubation or tracheostomy in neonates	12–18%
	Choanal stenosis/atresia	13–25%
	Cardiac malformation	11%
Very rare	Rachis malformation	7%
	Renal malformation	4%
	Microcephaly	3%
	Intellectual disability Delayed motor development	1.7–10%
	Limb anomaly	1.5%

Diagnosis of Treacher Collins syndrome

The diagnosis of TCS should be approached diligently as the multitude of clinical features could be confused for other craniofacial syndromes. The multifaceted nature of TCS requires a multidisciplinary approach involving geneticists, plastic surgeons, ophthalmologists, otolaryngologists, and many more healthcare providers. The syndrome was once believed to be a malfunction in the TOCF1 gene[21]; however, this hypothesis was later made to include mutations in POLR1D, POLR1C, and POLR1B as well.[18] Figure 2 depicts the approach toward TCS from the scope of malfunctions in the TOCF1 gene only.[21] When TCS is suspected, a TOCF1 mutation analysis is performed to detect any abnormalities. Should an abnormality be detected, the patient is confirmed to have TCS and is treated accordingly. Should the TOCF1 abnormality not be detected, the patient is then suspected to have some other form of craniofacial syndromes like Nager syndrome or Miller syndrome. Mutations in POLR1D, POLR1C, and POLR1B do not necessarily result in an autosomal dominant inheritance pattern, in contrast to the TCS1 subtype associated with a mutation in TOCF1. The heterozygosity of TCS emphasizes the importance of analyzing patients' family history and pedigrees.[28] The type of genetic testing performed depends on the clinical considerations of the patient and the available technologies; they include molecular genetic testing, chromosomal microarray analysis, next-generation sequencing, targeted mutation analysis, prenatal genetic testing, and array comparative genomic hybridization. Despite the effectiveness of genetic testing to confirm TCS diagnosis, clinical features should also be equally considered. Adolphe Franceschetti and

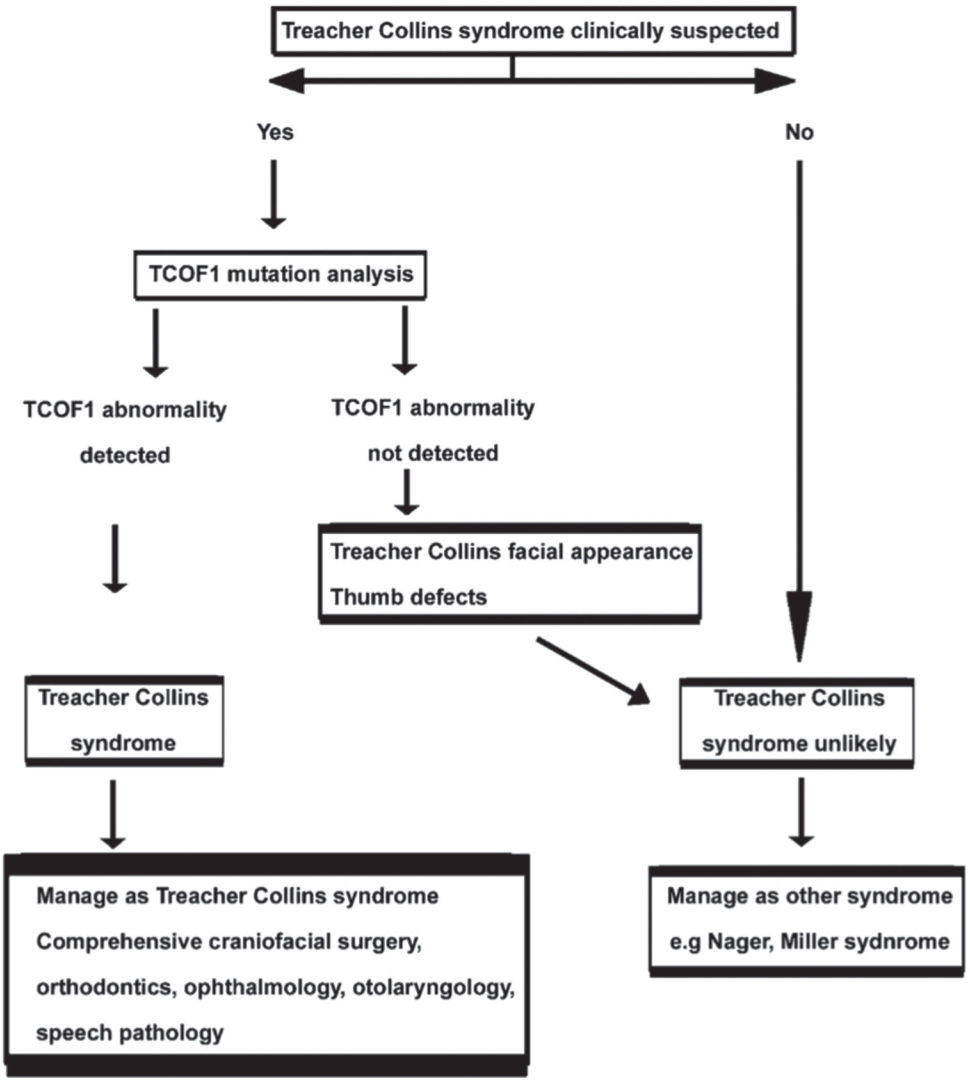

Figure 2: Approach toward TCS from the scope of genetic mutation

Jack Klein were notorious for dividing patients with TCS into five main categories depending on their clinical features.[29] These five types were as follows: (1) complete type presents with bilateral downward slanting palpebral fissures, hypoplasia of facial bones, especially mandible and zygomatic complex, and lower eyelid coloboma and microtia; (2) incomplete type presents with bilateral downward slanting palpebral fissures, hypoplasia of mandible and zygomatic bone, lower eyelid coloboma, and normal shaped external ears but with conductive hearing impairment; (3) truncated type only manifests eyelid deformities; (4) unilateral type; (5) irregular type.[27] Some other clinical features can be found in a study attempting to correlate phenotype and genotype in patients, including downward slanting palpebral fissures, malar hypoplasia, conductive deafness, mandibular hypoplasia, atresia of external ear canal, microtia, coloboma of the lower lid, asymmetry, projection of scalp hair onto lateral cheek, cleft palate, choanal stenosis/atresia, cardiac malformation, rachis malformation, renal malformation, microcephaly, intellectual disability, and anomaly of the limbs.[30] Another description of these clinical traits highlights malformation or underdevelopment of the patient's ears, affecting the shape and positioning of the ears.[31] The ear canal is often closed or not present, resulting in atresia. Alongside atresia, malformation of the ossicles often results in TCS patients experiencing bilateral conductive hearing loss.[32] Alternatively, this shows a patient suffering from unilateral hearing loss, who shared similar malformations.[33] The characteristic facial features of TCS patients also exhibit a downward slope of the eyelids, as opposed to the normal Mongolian slant, due to a condition known as antimongoloid slant.[34] Due to incomplete development, coloboma of the lower eyelid is also often reported with a lack of eyelashes observed in the gap area. As defined by Klein and Franceschetti, TCS is a craniofacial syndrome, oftentimes referred to as mandibulofacial dysostosis.[29] This secondary definition alludes to the underdeveloped nature of patients' jaws and cheekbones or in other words "hypoplasia of the mandible and zygomatic complex".[35] Another key characteristic depicted in the figure is the presence of hair in front of the ear. Patients also exhibit a distinct opening in the roof of the mouth, which occurs due to the failure of the palate tissues to fully fuse. Last, a vital aspect

to consider in the diagnosis of TCS is differential diagnosis.[36] Otodental syndrome, Nager syndrome, and Miller syndrome are very similar to TCS in terms of clinical features and can oftentimes only be differentiated through genetic testing. Figure 3 represents the differential diagnosis of some similar features.[37]

Treatment of Treacher Collins syndrome

The surgical management of TCS differs depending on the patient's age. Figure 4 highlights the possible surgical interventional methods.[27] Depending on the severity of the case, patients can require a series of surgeries, such as cleft palate repair, mandibulofacial reconstruction, zygomatic reconstruction, ear reconstruction, tracheostomy closure, eye surgery, and dental procedures. Each of these surgeries is associated with its potential drawbacks; for example, palatoplasty in TCS patients has a high incidence of velopharyngeal dysfunction (VPD).[38] The uniqueness of palatoplasty in TCS patients is further stressed on, where due to a high arch, smaller oropharynx, limited intrinsic opening, and thin, atrophic soft tissues, the operation in TCS patients is more difficult.[27] These challenges often call for the need of reoperation. Alongside a palatoplasty, dental intervention is frequently required to address malocclusion. Dental anomalies are very common in TCS patients, especially issues like hypodontia and anterior open bite, and upper teeth protrusion.[39] In terms of the repair of the zygomatic mandibular complex, the management of anomalous structures could be the answer to problems like airway obstruction. Common methods of intervention include mandibular distraction, an alternative to tracheostomy; however, surgery is recommended in severe cases. Some surgeons have utilized "size-matched stereolithographic templates derived from thin-plate spline warps".[40] These technologies provide better treatment for patients, hence resulting in improved outcomes. The main issues which arise in TCS patients are breathing, feeding, and hearing problems.[41] Besides surgical interventions to address these issues, alternatives such as hearing aids, speech therapy, and respiratory therapy are utilized. The literature shows that respiratory and positional therapy could help patients suffering from nonsevere breathing problems. Respiratory therapy involves continuous positive airway pressure (CPAP) to assist with breathing during sleep. Alternatives to CPAP include bilevel positive airway pressure (BiPAP), adaptive servo-ventilation (ASV), and positional therapy. Each of them addresses breathing problems differently, but they all aim to remedy the adverse effects which occur from obstruction due to anomalies. In regard to speech management, besides speech therapy, augmentative and alternative communication (AAC) could help patients struggling with effective communication. AAC involves the use of highly sophisticated speech generating devices, voice output devices, and picture exchange communication systems. Another technology, bone anchored hearing systems (BAHS), uses bone conduction to transmit sounds into the ears. The importance of long-term psychological support is an essential component in the management of TCS with studies highlighting the necessity of esthetic surgery.[40] Children cannot always undergo esthetic surgery during their pubescent years, making them susceptible to bullying. Studies investigating quality of life, mental wellbeing, and overall depression levels in individuals with conditions that affect the orofacial complex found that individuals with TCS reported the most severe depression, the least wellbeing, and the worst physical QoL.[42] These findings imply the strong need for psychosocial support these patients require. Efforts such as support groups could prove to be vital in improving the afflicted patients' quality of life and mental wellbeing. Psychosocial support, individualized toward each patient's anxiety, depression, and self-esteem issues, should be readily provided to patients with TCS. Early intervention is extremely essential because patients should not feel the sense of isolation for an extended period of time as it could severely affect their mental health. The literature does not provide studies directly correlating suicide rates with TCS patients; however, it does warn of the dangers lack of support could lead to.

Successful multidisciplinary care depends on multiple factors including frequent communication and collaboration among the care team, proactive monitoring and management of complications, and personalized treatment plans that address the patient's unique features. Starting from pediatrics, doctors perform proper assessments involving a detailed history taking, thorough physical examination, and radiological imaging of the skull and

Nager syndrome—generally sporadic in nature
- Mandible—more hypoplastic
- Downward slanting of palpebrae
- Cleft palate
- Scalp hair extending to cheek
- Rare lower lid colobomas
- Pre-axial limb abnormalities (hypoplastic/aplastic/duplicated thumbs, fused radius and ulna)

Miller syndrome
- Postaxial limb anomalies with absence/incomplete development of 5th digital ray of all four limbs
- Ectropion/out-turning of lower eyelids
- Cleft lip with or without palate

1st branchial arch syndrome
- Macrostomia
- Hemignathia
- Tragus abnormalities

Pierre Robin syndrome
- Retrognathia
- Glossoptosis
- Cleft palate

Oculo-auriculo-vertebral dysostosis
- Facial assymetry
- Flattened maxillary, temporal, malar bones
- Aplasia of condyle
- Ramus agenesis + macrostomia + lateral facial cleft + malocclusion
- Unilateral coloboma of upper eyelid
- Malformation of external ear
- Severe mental retardation

Figure 3: Differential diagnosis of TCS

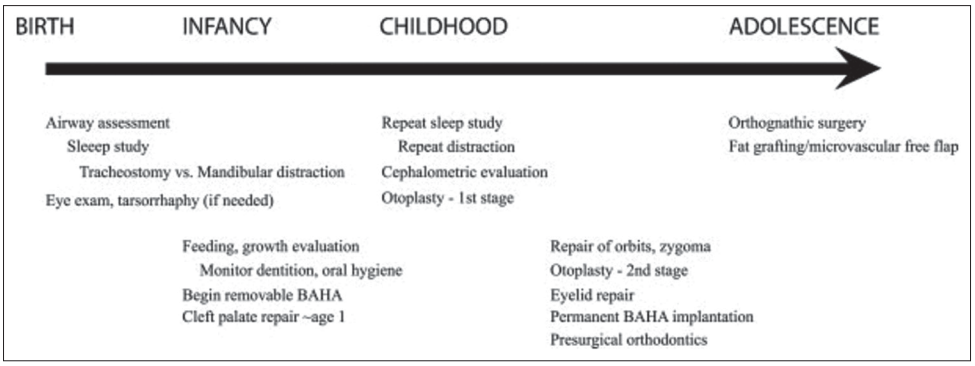

Figure 4: Management strategies

face. A previous case report demonstrated the importance of multidisciplinary teams for TCS patients, involving clinical genetics, otolaryngologists, orthodontists, audiologists, and psychologists. The case presented with poor nutritional status, lung infection, young age, and multiple surgical procedures needed for the case, ended with successful outcomes.[43] Furthermore, another case report demonstrated the importance of involving several healthcare professionals; initially, the geneticist reviewed the case and then referred it to ENT specialists for breathing problems resulting from abnormal facial structures. At 6 years old, surgical interventions from specialized surgeons have been done.[44]

Conclusion

Patients with TCS often present at birth with upper airway obstruction caused by craniofacial abnormalities. Other manifestations found include slanting eyes, ear deformities, depressed cheekbones, and cleft palate. Although there is no cure for this syndrome, treatment is directed to improve the quality of life. Craniofacial rehabilitation, tracheostomy, hearing aids, and speech language therapy can be used for these patients. Additionally, the disease can be associated with distress, anxiety, and depression. That makes psychological support an essential component of treatment plans.

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Conflicts of interest

There are no conflicts of interest.

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