NORD Guides for Physicians #12

The National Organization for Rare Disorders

The Physician's Guide to Treacher Collins Syndrome

NORD
National Organization for Rare Disorders

For more information about NORD's programs and services, contact:
National Organization for Rare Disorders (NORD)
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291
Website: www.rarediseases.org Email: orphan@rarediseases.org

NORD's Rare Disease Database and Organizational Database may be accessed at www.rarediseases.org.

This booklet is the twelfth in a series of free publications for physicians and other medical professionals. It is NORD's hope that patients and their families will benefit from this and other efforts to enhance awareness of the almost 7,000 rare diseases affecting an estimated 30 million Americans.

What is Treacher Collins syndrome?

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 a highly variable disorder. Mild cases can go unrecognized and undiagnosed, while severe cases can lead to serious, life-threatening respiratory complications.

TCS is estimated to affect approximately 1 in 10,000-50,000 individuals. The disorder is named after Edward Treacher Collins, a London ophthalmologist who first described the disorder in the medical literature in 1900. TCS is also known as mandibulofacial dysostosis or Treacher Collins-Franceschetti syndrome.

What causes Treacher Collins syndrome?

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.

Genetic diseases are determined by the combination of genes for a particular trait that are contained within the chromosomes received from the father and the mother. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or occurs as a new mutation in the affected individual. In 60% of TSC cases, the mutation is a new mutation without a positive family history of the disorder. However, a parent may be mildly affected and unaware that they have the disorder. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy.

Recessive genetic disorders occur when the same abnormal gene is inherited from both parents. The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy.

The *TCOF1* gene is located on the long arm (q) of chromosome 5, a region which is designated 5q32. *TCOF1* encodes a protein known as treacle. The exact role that treacle plays in the development of TCS is not fully understood. Researchers have determined that treacle plays a role in the creation of certain small structures found within cells that assemble proteins (ribosomes). Defects in ribosome biogenesis are termed ribosomopathies. *POLR1C* and *POLR1D* are located on chromosomes 6 and 12 respectively at positions 6q21.2 and 13q12.2. *POLR1C* and *POLR1D* encode subunits of RNA polymerases I and III, which are also essential for ribosome biogenesis. It seems likely that mutations in *POLR1C* and *POLR1D* also result in deficient ribosome biogenesis which is insufficient to meet the proliferation and growth needs of cells during development of the embryo. Because TCS is highly variable, researchers speculate that additional genetic and possibly environmental factors may also play a role in the variable severity of the disorder.

What symptoms are associated with Treacher Collins syndrome?

The specific symptoms present in TCS can vary dramatically from one person to another, even among members of the same family. TCS affects certain bones of the face, ears and around the eyes. These abnormalities are symmetrical (almost identical on both sides of the face). In some cases, serious respiratory complications can develop. It is important to note that affected individuals will not have all of the symptoms discussed below.

Underdevelopment of the cheekbones and nearby structures often results in a sunken appearance of the face and is described as malar hypoplasia with or without notching of the zygomatic bones. An abnormally small jaw may cause problems with swallowing or breathing. Children may be described as having features of "Robin Sequence" which include severe micrognathia, glossoptosis (a tongue that is displaced farther back in the mouth than normal) with or without cleft palate. Other airway problems such as blockage or narrowing of the nasal passages (choanal atresia or stenosis) or airway narrowing (pharyngeal hypoplasia) can compound the breathing issues of a newborn. Obstructive breathing problems including but not limited to sleep apnea can be dangerous and potentially cause neonatal death.

Approximately 5% of individuals with TCS display developmental deficits or neurological problems such as psychomotor delay. However, intelligence is generally unaffected with normal language development. Nonetheless, issues with speech development can occur because of hearing loss, cleft palate or difficulties producing sounds because of structural distortion.

Otological findings

Some people with TCS may have ears that appear normal. In others, the external ears may be abnormally small or completely absent. Otological findings potentially associated with TCS include;

- Absent, abnormally small or underdeveloped external ears
- Malformed external ears
- Atresia or stenosis of the external auditory canals
- Conductive hearing loss (ranging from mild to severe) usually due to malformations of structures within the middle ear

Ophthalmic findings

Eye abnormalities associated with TCS can give affected individuals a saddened facial appearance. Lower eyelid abnormalities can cause the eyes to dry out, which increases the risk of eye infection. Specific ocular abnormalities associated with TCS include;

- 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
- Drooping eyelids
- Vision loss
- Narrowed tear ducts (dacrostenosis)

Dental findings

Approximately 60% of individuals with TCS may develop dental abnormalities including;

- Missing teeth (tooth agenesis)
- Discoloration of the teeth (enamel opacities)
- Widely-spaced teeth
- Abnormal eruption of certain teeth (ectopic eruption of maxillary first molars)
- Malocclusion (improper positioning of the teeth and jaw)

Additional symptoms and physical features may be associated with TCS. These findings occur less frequently and can include;

- A highly arched roof of the mouth (palate)
- Cleft palate
- Nasal deformity
- Widely spaced eyes
- Notching of the upper eyelid
- An abnormally wide mouth (macrostomia)
- Abnormal scalp hair pattern (front of the ears and extending toward the cheeks)
- Congenital heart defect

How is Treacher Collins syndrome diagnosed?

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.

Molecular genetic testing to confirm a diagnosis is available through commercial and academic research laboratories to detect mutations in the *TCOF1*, *POLR1C* and *POLR1D* genes. Approximately 90-95% of individuals have an identifiable mutation of the *TCOF1* gene.

Prenatal diagnosis is possible through chorionic villus sampling or amniocentesis if a *TCOF1*, *POLR1C* or *POLR1D* gene mutation has been identified in an affected family member. Prenatal screening via ultrasound during mid-to-late gestation may detect cases with severe craniofacial abnormalities.

Relatives, especially parents and siblings, of an individual diagnosed with TCS should be carefully examined because mild cases often go unnoticed and undiagnosed.

How is Treacher Collins syndrome treated?

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. Genetic counseling is recommended for affected individuals and their families.

Specific therapies and surgeries depend upon several factors including age, extent or severity of the disorder, overall health and personal preference. For example, different abnormalities may be treated at different ages.

- Cleft palate – around 1-2 years of age
- Zygomatic and orbital reconstruction – around 5-7 years of age
- External and inner ear reconstruction – around 6 years of age
- Jawbone lengthening or reconstruction – range from newborn to teenage depending upon the extent and severity of the condition.

Craniofacial

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). Surgical reconstruction may also include small implants or fat injections to mask the severity of a craniofacial malformation.

Obstructive airways can be a serious problem not always obvious to parents or clinicians. A sleep or nap study may be used to help determine the severity of the obstruction and may influence the treatment plan. In severe cases, newborn infants may require intubation, an immediate tracheotomy or early mandibular distraction. Insertion of a gastrostomy tube may be necessary to ensure proper nutritional intake while protecting the airway.

Multiple surgeries may be required to treat the various craniofacial abnormalities that are potentially associated with TCS. Despite the number of surgeries, results vary from one person to another and the end result is rarely fully corrective.

Otological

Assessment of an infant's hearing is critical. A full assessment should be done early during life, even before one year of age and then yearly, in order to ensure proper speech development.

Surgery to the middle ear may be an option to restore hearing in some cases. However, surgery is not required or beneficial in all cases. Some individuals may benefit from bone-anchored hearing aids that augment or restore hearing. Some individuals may benefit from surgical implantation of this type of hearing aid. Speech therapy and educational intervention may also be used to help individuals with hearing loss.

Reconstruction of the external ear, external auditory canal and the middle ear may be necessary in some cases for functional or cosmetic purposes. Generally, reconstruction of the external ear should be performed first.

Ophthalmologic

Ocular abnormalities may be treated with corrective lenses, contact lenses and other supportive techniques. Eye ointments may be used, especially at night, to prevent the eyes from drying out during sleep.

Surgery may be necessary to correct a lower lip coloboma or to help with vision problems because of misaligned eyes (strabismus). In some cases, individuals may undergo surgery to correct drooping eyelids, which can help prevent the eyes from drying out and lower the risk of infection. Eyelid surgery may also help to improve the facial expression. Obstructed tear ducts may also require surgery in some cases.

Dental

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.

Anesthesia Considerations

Structural airway problems associated with TCS can make it difficult for anesthesiologists to manage and maintain an airway during surgery. Proper evaluation including a comprehensive preoperative assessment and complete clinical history should be performed to best plan an anesthetic strategy.

Patient Support and Resources

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55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968
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Fax: (203) 798-2291

www.rarediseases.org
orphan@rarediseases.org

NORD gratefully acknowledges the assistance of the following medical experts in the preparation of this booklet:

Dr. Paul Trainor
Stowers Institute for Medical Research,
Kansas City, MO 64110, USA

Dr. Pedro A. Sanchez-Lara
Children's Hospital Los Angeles
University of Southern California
Los Angeles, CA 90027, USA

Dr. Michael Dixon
University of Manchester,
Manchester, M13 9PT, UK

NORD Guides for Physicians #12

#1 The Pediatrician's Guide to Tyrosinemia Type 1

#2 The Pediatrician's Guide to Ornithine Transcarbamylase Deficiency...and other Urea Cycle Disorders

#3 The Physician's Guide to Primary Lateral Sclerosis

#4 The Physician's Guide to Pompe Disease

#5 The Physician's Guide to Multiple System Atrophy

#6 The Physician's Guide to Hereditary Ataxia

#7 The Physician's Guide to Giant Hypertrophic Gastritis and Menetrier's Disease

#8 The Physician's Guide to Amyloidosis

#9 The Physician's Guide to Medullary Thyroid Cancer

#10 The Physician's Guide to Hereditary Angioedema (HAE)

#11 The Physician's Guide to The Homocystinurias

#12 The Physician's Guide to Treacher Collins Syndrome

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from www.rarediseases.org.

This booklet was made possible through a bequest from the estate of Joanne P. Robinson.

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's web site at www.rarediseases.org or call (800) 999-NORD or (203) 744-0100.

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

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