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Review

MICROTIA IN TREACHER COLLINS SYNDROME: A REVIEW ARTICLE

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ABSTRACT

Background: Treacher Collins Syndrome (TCS) is a condition affecting the development of facial structures. TCS presents with variable clinical manifestations and can impact the quality of life of those affected. Early identification and diagnosis are crucial management planning and intervention.

Objective: To understand the embryology, genetic abnormalities, and manifestations of TCS which would facilitate the diagnosis.

Methods: A narrative review of the literature published between 2010 and 2024. The literature search was conducted using the keywords "Treacher Collins Syndrome" and related terms (embryology, epidemiology, diagnosis) across academic databases such as PubMed, Google Scholar, and ScienceDirect.

Results: From the 116 articles identified, a review was conducted on 23 publications deemed relevant and appropriate to the topic. Treacher Collins Syndrome (TCS), also known as Mandibulofacial Dysostosis, is a genetic disorder affecting facial structures, characterized by variable clinical manifestations. TCS has impact on the quality of life of those affected. It is inherited in an autosomal dominant manner and involves mutations in the TCOF1, POLR1D, POLR1C or POLR1B genes, which disrupts the development of the pharyngeal arches during embryogenesis. Microtia and conductive hearing loss are otology manifestations of TCS. TCS is diagnosed based on clinical manifestations, along with genetic confirmation.

Conclusion: Identification and diagnosis of Treacher Collins Syndrome (TCS) are crucial for planning management and interventions that can improve the patient's quality of life.

Keywords: Microtia, Treacher Collins Syndrome, Mandibulofacial dysostosis, conductive hearing loss

INTRODUCTION

Treacher-Collins Syndrome (TCS) is a genetic disorder characterized by craniofacial deformity including microtia, it is a condition in which the external ear is not completely developed. Microtia is prevalent in TCS, accounting for 85 – 96% of TCS cases and it is closely related to auditory function.[1,2] Treacher-Collins Syndrome is a rare genetic prevalence with an estimated prevalence of 1 in 50,000 live births. It does not have gender predilection. The mode of TCS gene mutation inheritance is autosomal dominant but 60% of TCS cases occur due to de novo mutation in which the mutation occurs spontaneously without any familial history. The TCS cases have no association with certain races or ethnicity, and the birth malformation rate is relatively stable and non- progressive. It is commonly diagnosed shortly after birth due to facial deformities although in mild cases the diagnoses are late until the children have other difficulties including hearing or respiratory disorders.[2] Further understanding of microtia in TCS may also provide knowledge about genetic mechanisms and the underlying development of this condition that can assist clinicians in early diagnosis and appropriate intervention.

METHODS

The narrative method of TCS literature was used in this literature review. We used several such as Treacher-Collins Syndrome and other relevant words (embryology, epidemiology, diagnosis, and differential diagnosis) in several databases, PubMed, Google Scholar, and ScienceDirect. The inclusion criteria of the literature were: Indonesian or English TCS, microtia, or ear embryology literature; published in the last 15 years (2010 – 2024); and randomized controlled trial, case report literature review, systematic review, or meta-analysis. The exclusion criteria were literature that is not available in the full paper and article that does not clearly discuss TCS, microtia, and ear embryology.

The full paper assessment was conducted following the initial abstracts' screening using the inclusion and exclusion criteria. Twenty-three eligible and relevant articles were included in this review (Figure 1).

Table 1 below contains the results of the literature search used in this article review to serve as a comprehensive guide to the references analyzed.

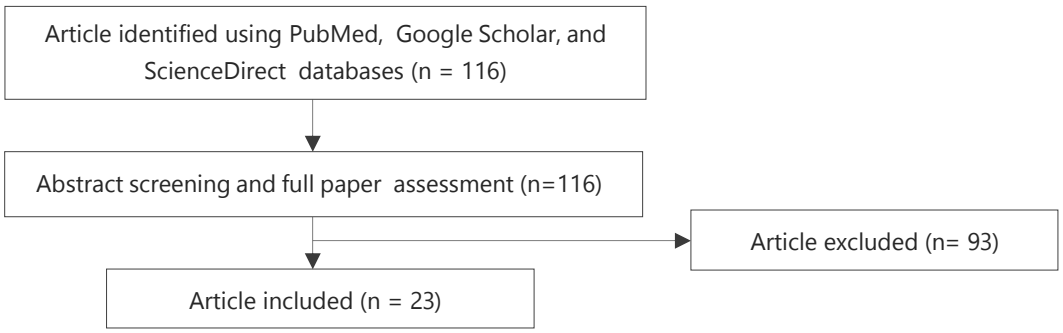

Figure 1. The Article Selection Process

Table 1. The Summaries of Included Studies

Authors	Year	Summaries
Goodgellow et al.[6]	2013	RNA Polymerase (Pol) I produces ribosomal (r)RNA, an essential component of the cellular protein synthetic machinery that drives cell growth, underlying many fundamental cellular processes.
Renju et al.[15]	2014	Auricular malformation is one of the most common clinical features of TCS.
Sakai et al.[7]	2016	External ear abnormality is one of the characteristic abnormalities in TCS.
Vincent et al.[11]	2016	Microtia is one of the most common clinical features of TCS. It is found approximately in 57.1 – 78% of TCS and associated with conductive hearing loss.
Plomp et al.[16]	2016	TCOF1, POLR1D, or POLR1C mutations are responsible for craniofacial deformities in TCS including microtia.
Sharma et al.[17]	2016	External ears abnormalities, external auditory canals atresia, and middle ear ossicles malformation in TCS are bilaterally symmetrical and result in bilateral conductive hearing loss.
Van et al.[22]	2017	CHARGE syndrome is a multiple congenital anomaly condition caused, in a majority of individuals, by loss of function pathogenic variants in the gene CHD7
Ulirsch et al.[21]	2018	Diamond-Blackfan anemia (DBA) is a rare bone marrow failure disorder that affects 7 out of 1,000,000 live births and has been associated with mutations in components of the ribosome.
Fan et al.[12]	2019	TCOF1 mutation accounts for 70 – 93% of TCS cases and it is inherited via an autosomal dominant pattern. The pathogenic variants of TCOF1 gene can be found in the family members of TCS.
Veugen et a[15]	2020	Microtia is a broad term that encapsulates a diverse array of auricle abnormal appearance, it is the mildest expression of oculo-auriculo-vertebral spectrum and the most common external ear abnormalities.
Sanchez et al.[8]	2020	POLR1B gene is a causative gene of TCS, particularly TCS4. Its' pathogenic variant leads to abnormal neural crest cell differentiation and migration that is associated with external ear canal atresia.
Kantapura et al.[13]	2020	Treacher-Collins Syndrome patients may be clinically normal but radiologically abnormal. TCOF1 plays important roles in the ear development even in the later stages.
Liu et al.[14]	2020	TCOF1 gene mutation is the most mutations reported in TCS patients. Ear malformations are commonly associated with bilateral conductive hearing loss.
Marszalek-K[9]	2021	Microtia with conductive hearing loss commonly occurs due to ossicles malformation.
Grzanka et al.[10]	2021	TCOF1 haploinsufficiency is associated with TCS through ribosome biogenesis disruption that leads to p53 activation. Neuroepithelial and neural crest cells proliferation will be reduced due to p53 activation.
Zhang et al.[18]	2021	Treacher-Collins Syndrome is a rare autosomal dominant or recessive disorders. Stenosis or atresia of external ear are commonly found in TCS patients.
Dragoi et al.[19]	2021	Mandibular dysostosis Guion-Almeida type (MFDGA) is one of the differential diagnoses of TCS and both have microtia as one of their clinical manifestations.

Table 1. *Continue*

Authors	Year	Summaries
Varadarajan et al.[23]	2021	Pierre Robin syndrome/sequence (PRS) is associated with a triad of symptoms that includes micrognathia, cleft palate, and glossoptosis that may lead to respiratory obstruction.
Marszale-Kruk et al.[2]	2023	Ears reconstruction can be done even in the late childhood by creating new ear replications based on the second ear or the parent's ear, but it only improves the appearance, not the hearing function.
Helwany et al.[3]	2023	A classic indicator of Treacher-Collins Syndrome (TCS) is bilateral microtia, it is present in approximately 85% TCS patients.
McElrath et al.[1]	2024	Microtia is one of the most common clinical manifestations of Treacher-Collins Syndrome, it is usually symmetrical and bilateral.
Universitaat Fribourg Switzerland Face and Upper Foregut[4]	2024	Ears arise from the pharyngeal portion of the foregut, particularly between the first and second pharyngeal arches.
National Human Genome Research Institute[20]	2024	Treacher-Collins Syndrome 1 and 4 are inherited in autosomal dominant pattern. On the other hand, TCS3 is inherited in autosomal recessive pattern. Treacher-Collins Syndrome 2 can be inherited in autosomal dominant or recessive pattern.
Goodgellow et al.[6]	2013	RNA Polymerase (Pol) I produces ribosomal (r)RNA, an essential component of the cellular protein synthetic machinery that drives cell growth, underlying many fundamental cellular processes.

RESULTS

Treacher-Collins Syndrome (TCS) is a rare genetic disorder, affecting facial structural development, size, shape, and position. It is also known as Mandibulofacial Dysostosis with an estimated prevalence of 1 in 50,000 live births. The clinical manifestation in TCS ranges from mild to severe due to variable phenotypes and they can significantly affect patients' quality of life.[1]

Embryology

Treacher-Collins Syndrome affects craniofacial structure development including facial bones, ear, and soft tissue. The embryology process defects in TCS occur from the 4th to the 7th week of development which is a critical period for 1st and 2nd pharyngeal arch formation. The disturbances in this arch development can result in the typical facial and ear malformation of TCS.3 The pharyngeal arch development is affected by various gene expressions including the TCOF1 gene. TCOF1 mutation can result in various malformations one of which is microtia.[3,4] The external ear development including auricula (pinna) is one of the most significant processes. It is directly related to "Hillocks of His" which is formed from neural crest cell migration and has a role as a pioneer of external ear structure.3,6 The hillock of His and external ear structure formation is regulated by various genetic factors and molecular signals. TCOF1 gene- encoded protein will direct the migration and proliferation of neural crest cells.[2-6]

Pathogenesis and Genetic Variance in Treacher-Collins Syndrome

Treacher-Collins Syndrome is an autosomal dominant inherited genetic condition with TCOF1 as the main involved gene that accounts for more than 90% of TCS cases. TCOF1 gene encodes treacle protein that plays a role in ribosome and ribonucleic acid (RNA) ribosomal synthesis during initial embryology development, also maintaining the stability and function of neural crest cells. The TCOF1 gene mutation leads to decreased treacle production that causes impaired neural crest cell migration and proliferation in the craniofacial area. This leads to facial bones hypoplasia, ear deformities, and other malformations that are characteristics of TCS.[7-10]

Neural crest cell deficiency leads to mandibula hypoplasia, external ear malformation, and other associated structures. These cells are more prone to apoptosis when the treacle production is impaired. As a result, the amount of neural crest cells is not sufficient for craniofacial structural normal development and it leads to the clinical manifestation of TCS.[7-11] There are several clinical subtypes of TCS:[2,9]

1. Treacher Collins Syndrome 1 (TCS1): Pathogenic variant of TCOF1 gene.
2. Treacher Collins Syndrome 2 (TCS2): Pathogenic variant of POLR1D gene.
3. Treacher Collins Syndrome 3 (TCS3): Pathogenic variant of POLR1C gene
4. Treacher Collins Syndrome 4 (TCS4): Pathogenic variant of POLR1B gene.

Table 2. The Gene Classification and Treacher Collins Syndrome Subtypes[2]

TCS Subtypes	Frequencies	The production from:
TCS1	86%	Treacle protein
TCS2	6%	DNA-directed RNA polymerase I and III subunit RPAC2
TCS3	1.2%	DNA-directed RNA polymerase I dan III subunit RPAC1
TCS4	1.3%	DNA-directed RNA polymerase I subunit RPA2

The pathogenic variant of the POLR1D gene is autosomal dominant and autosomal recessive, POLR1C gene was autosomal recessive while TCOF1 and POLR1B genes were autosomal dominant. The variants of POLR1D and POLR1C lead to gene haploinsufficiency and gene functional depletion, respectively.[2,12-14]

The TCOF1 gene encodes treacle protein. This protein is involved in protein and ribosome subunit transport between nucleolus and cytoplasm. It also supports ribosomal DNA gene transcription through the interaction with UBF. Treacle decrease can lead to rapid movement of UBF from rDNA and subsequently inhibit the rRNA synthesis. Increased treacle expression can impair cisplatin-induced apoptosis. Thus, inhibition of ectopic expression of TCOF1 code may lead to neural crest cell apoptosis during embryogenesis with the mechanism of action affecting the apoptosis regulator. The functional loss of treacle protein in neuroblastoma cells affects the expression of genes involved in proliferation, apoptosis, and cell cycle.[7,13,15] In the TCS cases, genetic mutation impairs the neural crest cells development will affect external ear development and may lead to microtia or anotia. A study revealed that most TCS patients with TCOF1, POLR1C, or POLR1D gene mutation have ear deformities with microtia as one of the most frequent disorders.[12,16]

Microtia and Hearing Disorders in Treacher Collins Syndrome

Microtia is a congenital disorder characterized by abnormal or incomplete external ear (auricle) development. It can occur unilaterally or bilaterally with various severity grades.[3] Microtia in TCS results from the imbalance between the development or fusion of hillocks of His so that hillocks are not completely developed or fail to fuse properly.[2,6]

In TCS, microtia is one of the most common clinical manifestations and become an important marker of TCS diagnosis. The most common ear manifestation of TCS involves pinna auricle disorders associated with atresia of external auditory canals and middle hearing bone anomalies. It Is estimated that 85 – 96% of TCS patients have microtia with various severity.[2,12,17]

Besides external ear deformities, microtia is frequently associated with conductive hearing loss due to ear canal atresia. The severity grade of microtia correlated with the severity of other TCS clinical manifestations such as conductive hearing loss and facial deformities. Microtia in TCS has various clinical manifestations, depending on the involved specific mutation and environmental factors that affect embryo development. Other factors such as maternal age, teratogenic exposure, and maternal health conditions during pregnancy also can affect the severity of microtia in TCS.[2,12,17] Bilateral conductive hearing loss is a common TCS manifestation (83 – 96%). Studies revealed 40 – 50% of TCS patients had bilateral conductive hearing loss. Several studies reported a higher prevalence of up to 85%, depending on the population studied and diagnostic methods.[16]

The severity of hearing disorders in TCS ranges from mild to severe. Conductive hearing disorders occur due to atresia of external auditory canals or moderate to severe ossicle malformation. The hearing disorders in TCS significantly affect communication and language development. Children with unidentified and not properly treated hearing loss are prone to speech delay and social development impairement.[2]

The Diagnosis and Differential Diagnosis of Treachers Collins Syndrome

The diagnosis of TCS is commonly made clinically because of its very distinctive physical characteristics. However, through evaluation and genetic confirmation remain important for accurate diagnosis and tailoring the proper management. The clinical manifestations of TCS are summarize in Table 3.[2,10,12]

Table 3. The Clinical Manifestations of Treacher Collins Syndrome[10]

Classical Characteristic	Symptoms	Frequencies
Very frequent	Eyelids with downward slant	89 – 100%
	Mala hypoplasia/ zygomatic complex hypoplasia	81 – 97%
	Conductive hearing disorders	83 – 92%
	Mandibula hypoplasia or micrognathia	78 – 91%
Frequent	External auricular canal atresia	68 – 71%
	Microtia	10 – 77%
	Coloboma	54 – 69%
	Speech disorders	57 – 63%
	Improper location of preauricular hair	24 – 49%
	Cleft palate	21 – 33%
	Choanal stenosis or atresia	13 – 25%
	Heart malformation	11%
Very rare	Spine malformation	7%
	Renal malformation	4%
	Microcephaly	3%
	Intellectual and movement development disorders	1.7 – 10%
	Extremity abnormalities	1.5%

TCS diagnosis can be classified into prenatal and postnatal. The prenatal diagnosis can be established with the evidence of micrognathia and microtia through ultrasonography examination during prenatal screening.

Three-dimensional ultrasonography imaging has been shown to detect these minor features including downward slant palpebra, micrognathia, and microtia.[2,10] Postnatal

diagnosis is commonly established through genetic tests by taking blood samples test for deoxyribonucleic acid (DNA) isolation from the patients or their family members based on the family history or facial characteristics. A genetic test is a gold standard to ensure TCS diagnosis.

The diagnosis is made through molecular genetic test and heterozygote pathogen variant detection (in an autosomal dominant inheritance pattern) in TCOF1 or POLR1D gene or biallelic pathogen variant (in an autosomal recessive inheritance pattern) in POLR1C or POLR1D gene. Genetic tests are not only for diagnosis confirmation but also for genetic counseling, particularly for families with a TCS history.[2,11,12]

Several additional tests may be required, including[2,10,17]

1. Audiometry to assess the severity or type of hearing disorder, particularly if ear malformations are found.
2. Radiology examination, such as X-ray, computerized tomography (CT) scan, or magnetic resonance imaging (MRI) for facial bony structure, middle ear, and other craniofacial bones assessment, that is important for surgery plan if reconstruction is required.
3. Nasopharyngeal endoscopy of upper respiratory tract evaluations, particularly patients with obstructive sleep apnea symptoms.

Several syndromes with microtia as one of their clinical manifestations are summarized in Table 4. Careful clinical examinations and genetic tests are critical to differentiate TCS from these conditions and confirm the precise diagnosis.[20-23]

Table 4. The Differential Diagnoses of Treacher Collins Syndrome with Microtia as Their Clinical Manifestation[10]

Syndrome	The difference with Treacher Collins Syndrome	Involved genes
Guion-Almeida[20]	Microcephaly, cognitive and motoric development delays	EFTUD2
Nager[2]	Syndactyly and clinodactyly	SF3B4
Diamond-Blackfan[22]	Macrocytic anemia and increased fetal hemoglobin	RPS28
CHARGE[23]	Tetralogy of Fallot, choanal atresia, atresia anal, cognitive and motoric development disorders	CHD7 / SEMA3E
Pierre Robin Sequence[24]	Glosoptosis and cleft palate	SOX9

CONCLUSIONS

Microtia is one of the most common clinical manifestations of TCS. The main etiology of TCS is mutation of TCOF, POLR1D, POLR1C, or POLR1B gene that affects the neural crest cells development during embryogenesis. It leads to an imbalance between hillocks of His formation or fusion so that hillocks are not completely developed or fail to fuse resulting in microtia. Although the clinical symptoms are often sufficient to predict TCS, genetic tests will provide definitive confirmation. Timely diagnosis allows for appropriate intervention planning to increase patients' quality of life.

Our review has several limitations, such as limited included articles in terms of number and language but the range of published years is quite long (2010 – 2024). The knowledge of diagnosis and treatment of TCS is required as a guideline for clinicians to improve the rate of timely diagnosis and appropriate treatment.

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