

## Risk factors for Microtia and preventive approaches

Fatores de risco para Microtia e abordagens preventivas

Factores de riesgo de Microtia y enfoques preventivos.

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### ABSTRACT

Microtia is a congenital anomaly that directly affects the external ear. Although the etiology of this pathology is not fully elucidated, there are several factors that are associated with its occurrence, such as genetics, perinatal and maternal conditions. During organogenesis of the outer ear it is important to mention that as anomalies occur before the sixth week of pregnancy, the chances of severe defects or total absence of the outer ear increase. At the genetic level, the etiology of microtia has been related to multiple causes, as well as the identification of genes involved in allelic expression pathways and transcription factors. Furthermore, this anomaly does not always occur alone, but associated with other pathologies such as cleft palate (12.8%), cleft lip and palate (11.5%), anophthalmia/microphthalmia (11.5%), facial asymmetry (10.6%), as well as oculoauriculovertebral spectrum syndromes, Goldenhar syndrome, craniofacial microsomia, Treacher Collins syndrome, Nager, DiGeorge or 22q deletion, Townes-Brock syndrome and branchi oto-renal syndrome. Treatments are based on the aesthetic management of the patient, but also related to the improvement of the patient's hearing ability. Epidemiologically, the prevalence ranges from 0.8 to 17.5 per 10,000 live births. One of the main risk factors for variation in case identification is altitude, genetics and maternal-perinatal factors. This literature review provides a thorough analysis of information for the better understanding, analysis and clinical management of this congenital anomaly.

**Keywords:** Microtia, genetic causes, anomalies.

### RESUMO

Microtia é uma anomalia congênita que afeta diretamente o ouvido externo. Embora a etiologia desta patologia não esteja totalmente elucidada, vários são os fatores que estão associados à sua ocorrência, como genética, condições perinatais e maternas. Durante a organogênese da orelha externa é importante mencionar que como as anomalias ocorrem antes da sexta semana de gestação, aumentam as chances de defeitos graves ou ausência total da orelha externa. No nível genético, a etiologia da microtia tem sido relacionada a múltiplas causas, bem como à identificação de genes envolvidos em vias de expressão alélicas e fatores de transcrição. Além disso, esta anomalia nem sempre ocorre isoladamente, mas associada a outras patologias como fenda palatina (12,8%), fissura labiopalatina (11,5%), anofthalmia/microftalmia (11,5%), assimetria facial (10,6%), também como síndromes do espectro oculoauriculovertebral, síndrome de Goldenhar, microsomia craniofacial, síndrome de Treacher Collins, deleção de Nager, DiGeorge ou 22q, síndrome de Townes-Brock e síndrome branchi oto-renal. Os tratamentos são baseados no manejo estético do paciente, mas também relacionados à melhora da capacidade auditiva do paciente. Epidemiologicamente, a prevalência varia de 0,8 a 17,5 por 10.000 nascidos vivos. Um dos principais fatores de risco para variação na identificação de casos é a altitude, a genética e os fatores materno-perinatais. Esta revisão de literatura fornece uma análise minuciosa de informações para melhor compreensão, análise e manejo clínico desta anomalia congênita.

**Palavras-chave:** Microtia, causas genéticas, anomalias.

### RESUMEN

La microtia es una anomalía congénita que afecta directamente al oído externo. Aunque la etiología de esta patología no está totalmente dilucidada, existen varios factores que están asociados a la ocurrencia de la misma, tales como genética, condiciones perinatales y maternas. Durante la organogénesis del oído externo es importante mencionar que a medida que las anomalías se presentan antes de la sexta semana de embarazo, las probabilidades de defectos graves o ausencia total del oído externo se incrementan. A nivel genético, la etiología de la microtia se ha relacionado a múltiples causas, así como la identificación de genes involucrados en las rutas de expresión alélica y factores de transcripción. Además, que esta anomalía no siempre se presenta sola, sino asociada con otras patologías tales como paladar hendido (12,8 %), labio y paladar hendido (11,5 %), anofthalmia/microftalmia (11,5 %), asimetría facial (10,6 %), así como síndromes del espectro oculoauriculovertebral, el síndrome de Goldenhar, microsomía craneofacial, síndrome de Treacher Collins, Nager, DiGeorge o delección 22q, síndrome de Townes-Brock y síndrome branqui oto-renal. Los tratamientos se basan en el manejo estético del paciente, pero también relacionado con la mejora de la capacidad auditiva del mismo. A nivel epidemiológico, la prevalencia oscila entre 0.8 a 17.5 por 10.000 nacidos vivos. Siendo uno de los principales factores de riesgo para la variación en la identificación de casos la altitud, genética y factores materno-perinatales. Esta revisión bibliográfica provee un análisis de información minucioso para el mejor entendimiento, análisis y manejo clínico de esta anomalía congénita.

**Palabras clave:** Microtia, causas genéticas, anomalías..

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### ARTICLE INFORMATIONS

#### Science-Metrix Classification (Domain):

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#### Main topic:

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#### Main practical implications:

The article offers a robust overview of the state of the art in studies that analyze the pathology Microtia and its main risk factors and preventive approaches. The results can contribute with new research or even the design of public policy.

#### Originality/value:

The article is relevant and original because it discusses in perspective a pathology not widely commented on by Latin American medical literature.

## INTRODUCTION

Congenital anomalies are one of the leading causes of perinatal and neonatal death in both underdeveloped and developing countries. (1). These malformations have multifactorial etiologies and 40% of the cases are idiopathic, but there is evidence that they are more frequent in populations with consanguineous marriages(2). Many factors may be associated as a cause of congenital anomalies, such as environmental, genetic, teratogen exposure. The process of development of a child from a fertilized egg involves a number of steps, and some of them may generate complications, resulting in a defect in the gestational process. (3). Taking into account that the upper extremities are formed between the fourth and sixth week of pregnancy, it is estimated that one in twenty newborns may have a chromosomal or genomic anomaly. (4).

The World Health Organization (WHO) estimates that a total of 270,000 newborns die within 28 days of birth each year, of which congenital defects or anomalies are the fourth leading cause of death in these children. Importantly, postnatal complications, preterm delivery, neonatal infections, low birth weight, increased maternal parity, acute maternal illness, and medication use are all associated with neonatal death. (5). Some inherited disorders can skip generations and manifest in offspring when each parent transmits a recessive gene to the offspring. In addition, some teratogenic drugs, chemotherapeutic agents, thalassium, radiation exposure, alcohol and tobacco use in pregnant women also cause congenital defects. (3).

Within the congenital alterations of the external and middle ear, microtia and atresia/stenosis of the external auditory canal, are usually unilateral, more common on the right side, in this regard, for microtia 15% of its occurrence is related to the genetic syndromes of Goldenhar, Treacher, Collins, on the other hand, the incidence of atresia, according to different authors, varies from 0.92 to 1.72 per 10.000 live newborns, this variability is due to differences in diagnostic standardization and in the timing of studies performed on these patients in different countries.(2)

Microtia also has a higher incidence in countries at higher altitudes, there is an association between maternal diabetes and this pathology which occurs in 1 in 10,000 to 20,000 live newborns, this congenital anomaly is the most common in Asian and Hispanic populations and in Ecuador the incidence of microtia is 1 per 6,000 to 12,000 births and occurs more in boys than girls. (6).

## METHODS

The present research is a non-experimental review study, which collects information from articles, using keywords such as "microtia", "Atresia", "congenital malformations", "teratogenic drugs usage", "folic acid supplementation", "including abnormal pregnancy history", "hereditary diseases" that have been taken from different indexed journals and databases such as: PubMed, Medline, Scielo, Scopus, JAMA, UpToDate, Cochrane, ELSEVIER. In some cases, reference books were used to extend the bibliographic sources of consultation

## MAIN THEORETICAL FINDINGS

### A. Microtia

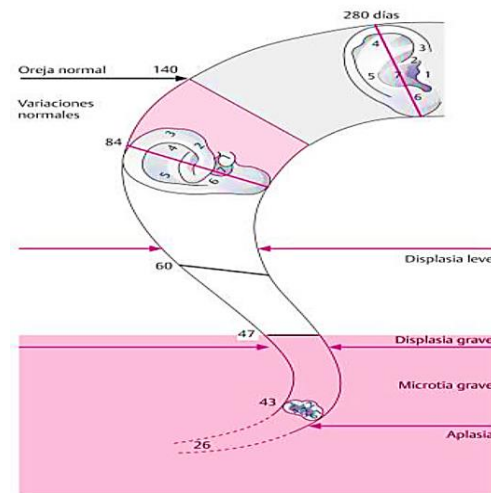
Etymologically it means "small ear", but is frequently used when referring to a spectrum of ear deformities that almost always occur in association with aural atresia (absence of an external auditory canal). Microtia encompasses a spectrum of congenital abnormalities of the pinna that range in severity from mild partial structural anomalies to complete absence of the ear (anotia). This condition presents aesthetic concerns for the child and family, and may induce secondary psychological sequelae associated with it, the ear deformity due to microtia is associated with the absence of the external auditory canal, which may present hearing problems, when the involvement is bilateral is associated with significant delays in language.

### B. Organogenesis

During normal embryonic development, the tissues of the future auricle are formed from the mesenchyme surrounding the first ectodermal pocket, from gill arches I and II, the first rudiments of the ear cartilages appear between 20-22 weeks of fetal development (7)At 27-28 weeks, the sensory part of the hearing aid is formed earlier, so that the sound-sensing structures are affected much less frequently; by 27-28 weeks, the conchae already have the appearance and shape of a newborn baby. It is believed that developmental disruption due to the influence of teratogens may occur at any of the above periods, however, it is suggested that the existence of a pattern in the occurrence of these more severe anomalies will be seen in the future, it is worth mentioning that anomalies that occurred before the sixth obstetric week are often

accompanied by severe defects or a complete absence of not only the outer ear, but also the middle ear (8) (9).

**Figure 1.** Changes in the developing pinna as it migrates during embryonic development, according to Leibery's description of typical malformations associated with embryonic development. 1, 2 and 3: auricular prominences of the first branchial arch. 4, 5 and 6: auricular prominences of the second branchial arch. 7: first gill cleft. **(Spanish illustration)**



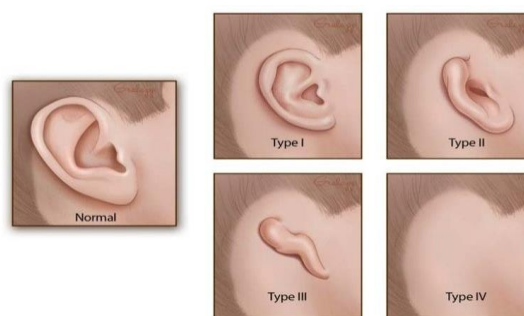
Source: Taken from (Weerda, Diseases of the external ear., 2019).

### C. Ranking

The Hunter classification is currently used according to severity in increasing order. (10):

- Grade I: slightly small ear with identifiable structures; small but present external auditory canal
- Grade II: partial or hemiear with an occluded or stenotic external auditory canal resulting in conductive hearing loss.
- Grade III: absence of the external ear with a small peanut-like vestigial structure and absence of the external auditory canal and eardrum.
- Grade IV: complete absence (anotia).

**Figure 2.** Hunter classification



Source: Hunter *et al*

### D. Etiology

Although the causal risk factors for this pathology have not been elucidated, results of cross-sectional studies include low birth weight, use of medications during the gestational period, maternal diabetes mellitus, higher maternal parity, advanced maternal age, multiple births, lack of folic acid supplementation and certain characteristics of Hispanic ethnicities are the triggers for this malformation (12).

In some clinical trials, it has been identified that the use of drugs at gestational age increases microtia including teratogens such as immunosuppressants, thalidomine, mycophenolate and in turn it has been reported that alcohol consumed in pregnancy unconsciously show microtia. (11). Another factor that affects children to develop microtia is the location of the Andean populations in Ecuador, which are located at an altitude of 2,500 meters above sea level (m.a.s.l.). Studies carried out in these populations associate microtia and the altitude of the localities of the Andean populations in

South America (6) (12).

### E. Causes

The main reason for the embryogenesis of the outer ear structures is the negative external influence on the development of the fetus during pregnancy. Hereditary microtia can be a component of one of the genetic syndromes: Nager, Treacher-Collins, Konigsmark, Goldenhar (8), (13). The most common teratogenic factors causing the development of the pathology include:

- TORCH infections.** This is the general name for infectious diseases in which there is a risk of intrauterine infection of the fetus and the formation of malformations. It includes toxoplasmosis, herpesvirus types 1, 2 and 3, rubella, syphilis, cytomegalovirus, parvovirus.(14)
- Physical factors.** These are usually ionizing radiation from X-rays or computed tomography, which are performed for health reasons or in case of undiagnosed pregnancy. This group also includes radiotherapy for oncopathologies, radioactive iodine treatment and prolonged hyperthermia.(15)(12)
- Bad habits.** The use of alcoholic beverages, narcotic substances (most often cocaine), tobacco products by a pregnant woman has a detrimental effect on the intrauterine development of a child.
- Pharmacological preparations.** Some drugs can cause congenital anomalies in a child. These are antibiotics (tetracyclines, penicillamine), antihypertensives (enalapril, captopril), iodine or lithium-based drugs, anticoagulants (warfarin), hormonal drugs (androgens).
- Endocrine pathologies.** These include diabetes mellitus in decompensation stage, phenylketonuria, folic acid deficiency, endemic goiter.

### F. Risk Factors

Intrauterine growth restriction and higher frequency of preeclampsia and fetal death are more common in high altitude populations than in low altitude populations. The uterine artery undergoes remodeling during pregnancy to accommodate increased maternal uterine artery blood flow and facilitates the delivery of oxygen and nutrients to the fetoplacental circulation. Chronic hypoxia is associated with residence at altitude, impairing maternal vascular adaptation to pregnancy, reducing the increase in uterine artery diameter and increasing its blood flow by about one-third (14) (16).

Populations living at high altitude experience intrauterine growth restriction and increased frequency of preeclampsia and fetal death, as the uterine artery undergoes remodeling during pregnancy to accommodate increased maternal uterine artery blood flow and facilitate oxygen and nutrient delivery to the fetoplacental circulation, whereby circulating levels of catecholamines and inflammatory cytokines are increased during the gestational stage in women living at high altitude. Andean peoples, in particular, are relatively protected against the reduction associated with increased fetal growth, which provides further support for the direct biological effects of altitude.(7)

Sometimes infant dysmorphologists claim that many types of congenital malformations are more common in multiple pregnancies, and that this may be due to a phenomenon called "fetoplacental steal" syndrome, when the placenta of a normal twin is usually larger than the placenta of an abnormal one. and perhaps there is an aggravation of the blood circulation of one of the twins, whose development is then interrupted.(9)

It is well known that deafness and sometimes microtia occur as a consequence of rubella during the first trimester of pregnancy. In addition, the use of certain medications during this critical period can also cause congenital disease (e.g., thalidomide, roaccutane (Accutane), clomid, retinoic acid). The influence of various external factors during the first trimester of pregnancy on the development of microtia in a child is not unequivocal, in 1-4% of cases it may be colds, measles, injuries, radiation, menstruation during the first trimester, hyperemesis. This clarification of what the term means I do not think it is necessary to do, review the general article and rectify, the presence of diabetes, emotional overload, alcohol consumption, anti-nausea drugs. the development of microtia is usually an occasional sporadic event, and it is important for parents to understand that the deformity was not caused by any action of the mother before or during pregnancy, and that the risk of recurrence in the family is about five percent, i.e., one in every twenty (12)(13).

### G. Genetic factors

A wide variety of patients with microtia (15 to 60%) have additional anomalies. Among 5 million live and non-live births, 818 cases were identified with at least one associated major congenital anomaly; these findings form the basis for defining specific syndromes. The most frequent congenital anomalies associated with microtia are cleft palate (12.8%), cleft lip and palate (11.5%), anophthalmia/microphthalmia (11.5%), facial asymmetry (10.6%), macrostomia (6.4%), preaxial polydactyly (2.2%), holoprosencephaly (2.2%) and epibulbar dermoids (1.7%).

The most common syndromes associated with microtia are oculoauriculovertebral spectrum (OAVS), Goldenhar syndrome (GS)/hemifacial microsomia/craniofacial microsomia (HCM), Treacher Collins syndrome, Nager, DiGeorge or 22q deletion, Townes-Brock syndrome (TBS) and branchio-oto-rena syndrome (BOR).(17)

#### Oculoauriculovertebral spectrum (OAVS)

OAVS is the most extensively studied microtia-associated syndrome, which is a complex heterogeneous disorder involving the first and second branchial arch derivatives. OAVS is broad, with anomalies including facial asymmetry resulting from maxillary and/or mandibular hypoplasia, preauricular or facial markings; ear malformations such as microtia, anotia, or aural atresia; and hearing loss. In a Turkish population with GS, microtia was present in 52 % of patients. Forty percent of patients with OAVS show strong allelic expression of BAPX1, a gene that belongs to the NK-2 family of transcription factors and plays an essential role in craniofacial development, BAPX1 abnormalities are present in patients' fibroblasts, suggesting that epigenetic dysregulation of BAPX1 plays an important role in this syndrome. (18)

#### Goldenhar Syndrome (GS)/Hemifacial Microsomia/Hemifacial Microsomia/Craniofacial Microsomia (HCM/CMF)

MCF is a congenital condition characterized by asymmetric hypoplasia of the craniofacial structures, most commonly including the mandible and ear. Heterozygous mutations in the EFTUD2 gene have been identified in a subgroup of patients with mandibulofacial dysostosis with microcephaly overlapping with SCD. A suggestive linkage to a region on chromosome 14q32 was found by whole genome linkage analysis in two families with features of SCD. The most interesting candidate gene in the linked region was GSC.(19)

#### Treacher Collins syndrome

Treacher Collins syndrome is an autosomal dominant disorder that presents phenotypically with hypoplastic facial bones, microtia, micrognathia, cleft palate, and hearing abnormalities.64 81 Mutations in the TCOF1 gene have been identified as the cause of Treacher Collins syndrome in up to 78% of patients. TCOF1 encodes a protein called molasses, which plays an active role in early embryonic development in the structures that develop into bones and other tissues of the face.(20)

#### Nager syndrome

Nager syndrome presents with micrognathia, external ear defects, external auditory canal stenosis, bilateral conductive hearing loss, cleft palate, down-slanting palpebral fissures, high nasal bridge, hypoplastic or absent thumbs, and variable toe and lower extremity defects. Most cases of Nager syndrome are sporadic, although both autosomal recessive and dominant familial cases have been described.(21)

#### DiGeorge syndrome

DiGeorge syndrome is one of the most common presentations of microdeletion associated with the 22.q11.2 deletion syndrome. (22)In most cases, the deletion removes 3 mbp of DNA encoding approximately 30 genes. Specifically, the human TBX1 gene, which is required for ear development and is expressed in multiple tissues during embryogenesis, is deleted. The features of DiGeorge syndrome include ear hearing abnormalities, craniofacial anomalies, hypoplasia of the thymus and parathyroid glands, and cardiac malformations. The ears are usually low-set, small, and with abnormal folding of the pinna.(23)

#### Townes-Brock Syndrome (TBS)

TBS is a rare autosomal dominant syndrome with a combination of anal, renal, limb and ear anomalies. TBS is caused by mutations in the SALL1 gene on chromosome 16q.4; TBS and OS have a significant number of overlapping features, including first and second arch defects and preaxial defects of the upper extremities. The phenotypic similarities between TBS and SG suggest that they may have a common genetic etiology.(24)

#### Branchio-oto-renal syndrome (BOR)

Branchial branchial syndrome (BOR) is an autosomal dominant developmental disorder characterized by branchial cleft cysts, atrial or external auditory canal anomalies, preauricular fossae, and hearing loss. BOR syndrome is diagnosed when BOS is accompanied by additional malformations of the kidney or urinary tract. Mutations in SIX1 and EYA1 have been shown to cause SBO, while mutations in SIX5 and EYA1 can cause BOR syndrome. Both are associated with microtia, among several other craniofacial defects.(25)(26)

Four genetic loci have been mapped for BOS/BOR4: BOR1, BOR2, BOS2, and BOS3. With the exception of BOS2, the corresponding genes have been identified. EYA1 was the first gene identified for BOR syndrome at the BOR1 locus and is found in approximately 40% of cases. (19).

## **H. Associated pathologies**

### Hearing loss

Embryologic development implies that microtia is often accompanied by middle ear pathology. In classic microtia, there is usually ear canal atresia and auditory ossicular disorders - Konigsmark syndrome (microtia, ear canal atresia and conductive hearing loss).(27) (28)

Middle ear deformities can range from a narrow canal and minor auditory ossicular disorder to hypoplastic fused auditory ossicles and poor aeration of the mastoid bone. It should be noted that since patients with atresia have ear canals like everyone else, they can cause middle ear inflammation (otitis media) even if they do not have an external auditory canal. Therefore, if this diagnosis cannot be confirmed by otoscopy, in case of suspected otitis media in the deformed ear, it is reasonable to prescribe antibiotics.(29)

### Pathology of the maxillofacial region

Since the pinna develops from the tissues of the branchial arches, it is not surprising that a large percentage of patients with microtia have deficient facial components that originate from these embryonic elements. The manifestation as a reduced half of the face, a condition known as hemifacial microsomia, is basically an underdevelopment of the jaws and overlying soft tissues. The more complete grade III genetic manifestation of this condition includes defects of the external and middle ear, hypoplasia of the upper and lower jaw, malar and temporal bones, macrostoma and lateral facial clefts, facial nerve palsy, atrophy of the facial and parotid muscles, even the palatal muscles may be weakened on the involved side.(30)

### Kidneys and urinary tract

Abnormalities of the urogenital tract are increased in the presence of auricular deformities, especially when the patient has other manifestations of facial underdevelopment. Some patients may have underdevelopment of the genitalia (hypospadias, agenesis of the female genitalia), various renal disorders (horseshoe kidney, unilateral renal agenesis, pelvic placement of the kidney, etc.). However, these anomalies do not cause life-threatening abnormalities of the genitourinary organs. Routine urinalysis may reveal latent hematuria or proteinuria, but most often shows nothing. In recurrent urinary tract infections in patients with microtia, investigation of renal function should begin with renal ultrasound before more invasive techniques are used to detect pathology. Because of the higher incidence of genitourinary tract disease in patients with microtia, it is advisable to perform periodic examinations with ultrasonography.(31)

### Cervical spine (neck)

Cervical spine anomalies are more frequent in patients with microtia when so-called midline defects, such as cardiac or renal disorders or cleft lip and palate, are present. Since associated neurological symptoms are rare, the incidence of these anomalies is quite low in patients with microtia. Goldenhar syndrome (oculoauriculovertebral dysplasia) is a condition in which an auricular defect is combined with the presence of a dermoid cyst of the eye and there is usually a cervical spine anomaly. If a patient with microtia is noted to have a dermoid of the eye or restriction of neck movement, renal function should be investigated and the cervical spine evaluated.(12)

### Diagnosis and physical examination

Diagnosis is made as soon as the newborn is born because approximately 20-60% of patients with congenital microtia are known to have associated anomalies or an identifiable syndrome, patients with microtia should be screened for other dysmorphic features. Physicians should take a complete history including ear infections, speech and language milestones, and family history of hearing loss and ear anomalies. Physical examination: A complete physical examination of the infant should be performed to look for associated syndromic findings. It is also critical to monitor the middle ear status in the typically formed ear to ensure that optimal hearing is maintained for the better hearing ear.(28)

Hearing screening: When infants have microtia and aural atresia, the affected ears will generally fail the newborn hearing screening test (NHS). Regardless of the NHS results, these infants should be referred directly to an audiologist for outpatient diagnostic auditory brainstem response testing. Newborn hearing screening is mandatory. Regardless of the presence or absence of an external auditory canal, an infant with microtia or severe aural malformation should be referred to a pediatric audiologist.(12)

## **I. Treatment**

The goals of treatment are the elimination of a cosmetic defect, improvement of hearing function and prevention of complications. The main method of its achievement is surgical. The choice of surgical intervention depends on the severity of microtia, the degree of development of the ear canal and concomitant dysplasia of regional bone structures. In the treatment of patients with congenital malformations of the external and middle ear, two main areas can be distinguished: improvement of hearing, aesthetic correction, and at the same time the psychological part will be of great help for these patients. (32) (31).

Types of hearing restoration operations:

Hearing aid implantation

If natural hearing restoration is not possible, the physician uses a special implant with bone fixation. The implant is a high-performance sound processor attached to a titanium plate. It is placed behind the affected ear, integrating with the skull bone. This implant is not implanted in children under 5 years of age; however, before the onset of operable age, the device can be attached to the head with a soft elastic bandage.(30)

Atresioplasty

This operation is indicated for the treatment of microtia associated with atresia and aims to restore normal hearing by opening and molding the ear canal. A rather complex surgical procedure performed by an otologist. For the treatment of congenital anomalies of the ear, as a rule, reconstructive otoplasty is used, designed to correct defects in the underdevelopment of the auricle or the consequences of its injury, up to restoration by total absence or after amputation. Modern technologies of reconstructive otoplasty allow complete restoration of the external ear.(29)

Rib Graft Reconstruction - Autologous Reconstruction

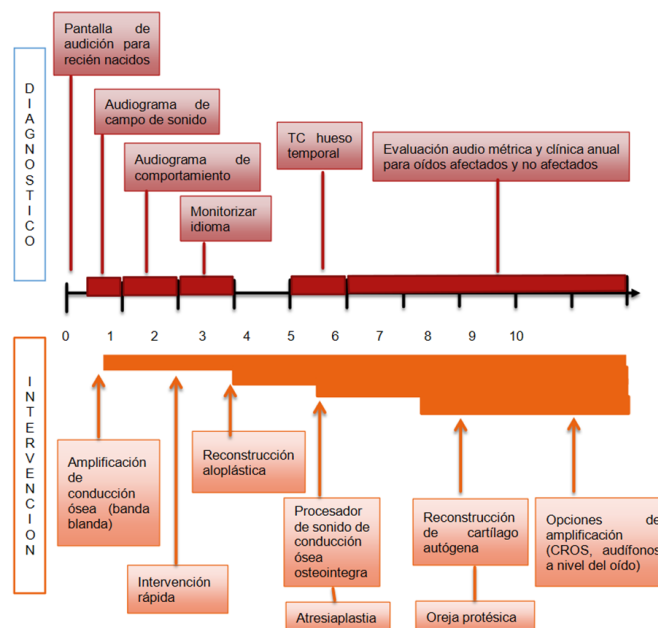
This procedure is the growth of the ear from the patient's own tissues. To do this, the surgeon removes fragments of the ear from the costal cartilage, producing a complete graft, which is then covered with a skin flap. The ear, made from the child's own tissues, is alive and grows with the child, remaining a natural part of the body. This type of operation is not performed on children under 6 years of age; this is due to an insufficient amount of costal cartilage. However, some more experienced surgeons can address this problem on an individual basis. An advantage of cartilaginous reconstruction is the extensive knowledge base that has been accumulated due to the wide use of this method worldwide. The reconstructed ear has sensation and vascularity compared with an alloplastic ear.(33)

Cartilage reconstruction allows for the creation of an individualized ear, which is carved by the surgeon to create symmetry with the opposite ear. This is ideal for various forms of microtia, particularly grades of microtia where part of the remaining ear can be saved, and part of the defect, as in grade II microtia. Sculpting the costal cartilage is a truly surgical art and a technically difficult task, also associated with modeling some similarity to the opposite ear. It should also be noted that, although the child after removal of the costal cartilage is left with a scar in the thoracic area, the use of own tissues in ear reconstruction is considered the gold standard.(34)

Ear prosthesis (artificial ear)

In some cases, if reconstruction is not possible, dentures are used. The dentures are made of soft, durable silicone. The impression for reproduction is taken from the second ear and hand-painted to match the patient's skin tone as closely as possible. The prostheses are attached with special glue, clips or magnets, as well as by osseointegration: attachment to titanium plates implanted into the bone at the natural site of the ear. Age restrictions for osseointegration: from 4 years of age. The bones of the child's skull must be strong enough for the operation.(12).

**Figure 3.**Chronology of diagnostic and treatment interventions for microtia and atresia **(Spanish illustration)**  
 Diagnostic studies are shown in blue and interventions in red. CROS, contralateral signal routing.



Source: Randall A. Bly, Murakami, & Sie, 2016.

**J. Epidemiology**

Birth prevalence is highly variable among some countries ranging from 0.8 to 17.5 per 10,000 live births. But variation in prevalence has been observed among Ecuadorians, Colombians, Bolivians, Chileans and Finns in a range of 0.3 to 4 per 10,000 births. (34).

The small or malformed ear tends to occur with an incidence of 1 to 10 per 10,000 births per year and in turn is often associated with syndromes in most cases occurs in isolation and unilaterally, with the right side being the most affected and in boys has a higher rate than in girls, in their ethnic groups occurs in Hispanics, Asians and Andeans. And in these occasions it is accompanied by atresia in 75% of the cases. (35).

Most of the cases this condition is a mutation with no identifiable cause, it is known that microtia has both genetic and teratogenic triggers, the teratogen that is associated with this cause is isotretinoin, more recent data proves that alcohol consumption during pregnancy and methamphetamine use increases the cases of microtia. The genetic basis is not well known, but it has been identified that it has a hereditary basis which is the treacher Collins syndrome (TCS) being an autosomal dominant inheritance pattern. (11).

**DISCUSSION**

Research data from Wales; have determined a prevalence of microtia of 1.11 per 10,000 newborns between the years 1998 and 2007; however, in the period 2000-2018, that value increased to 2.13 per 10,000 births. The more accurate detection rate of more than doubling the number of microtia diagnoses in this study was based on the use of data linkages to allow retrieval of information from a combination of secondary care inpatient and outpatient data in addition to primary care physician records. Although the overall incidence is comparable to epidemiological studies of predominantly Caucasian populations in California, USA (2.2 per 10,000 births) and Sweden (2.4 per 10,000 births), it is significantly higher than published rates for England (0-0.7 per 10,000 births) and Western Europe as a whole (0.88 per 10,000 births). The sex ratio in such a cohort (64% male: 36% female) is in line with contemporary European data from Finnish and German studies, in addition to ethnically heterogeneous populations in Japan, the United States, Venezuela, and Mexico.(36)(37)(38)

However, Table 1 shows a compilation of information on the prevalence of microtia across more than 90 global congenital disease surveillance programs in Europe, America, China, Australia, UAE and Japan, with higher prevalence observed in the hospital-based surveillance and active verification programs, which probably accounts for a proportion of the differences in prevalence. Importantly, three of the eight hospital-based programs are in South and Central America, and the Hispanic population has an apparently higher prevalence of microtia. In addition, microtia is an external anomaly, easily recognizable on postpartum physical examination; however, the less severe form of microtia is difficult to define and the term may be used with considerable variability in clinical settings and in medical records. This could lead to over- or under-reporting of microtia, resulting in an exaggeration of geographic variation in prevalence. (36)

**TABLE 1:** Prevalence (per 10,000 Births) and Prevalence Ratio of Microtia by Main Methodological Characteristics of Surveillance Program

	No. of programs	No. of cases	Prevalence (per 10,000 births)	Prevalence ratio	95% CI
Coverage					
Population-based	58	5089	1.68	1.00	Referent
Hospital-based	8	3828	2.97	1.77	1.70–1.85
ETOPFA <sup>a</sup>					
Reported	34	3975	1.84	1.00	Referent
Not reported	25	3141	1.74	0.95	0.90–0.99
Type of surveillance system <sup>b</sup>					
Active	11	1902	2.48	1.00	Referent
Passive	13	630	0.94	0.38	0.35–0.41

Source: Luquetti, D.V., Leoncini, E. and Mastroiacovo, P. (2011).

On the other hand, from the anthropological point of view, several studies emphasize that the variability by region or country, the incidence and clinical management of microtia is independent of the influence of socioeconomic deprivation and, given the homogeneity of the population, is unlikely to be related to ethnicity.(8)(12)



## FINAL CONSIDERATIONS

In general terms, from the point of view of genomic analysis, the process of outer ear formation involves the use of several molecular mechanisms, as well as regulatory genes and proteins that are fundamental for a successful formative process. For this reason, it is imperative to deepen the research parameters not only in the socio-epidemiological field to determine anthropological causalities, but also in the field of molecular and translational medicine so that the diagnosis, treatment and correction of this congenital anomaly have a correct mapping, genetic causalities and an adequate knowledge of the behavior of this pathology in Ecuador.

The genetic and cellular mechanisms associated with normal outer ear morphogenesis are not completely understood. A better understanding of the molecular mechanisms and processes of normal ear development will help to elucidate abnormal ear development that results in microtia and other ear anomalies. This study is the first stage for the diagnosis and future work on the knowledge, epidemiology and clinical management of microtia in Ecuador. Although it is true that there are no concrete data in the country about this congenital anomaly, it has been verified in medical consultations or interventions that many health professionals do not know about the etiology, management and distribution of this pathology in newborns. For this reason it is fundamental that this is the first step for a socialization and medical update on this case.

Although many genetic causes of microtia have been identified, with the development of animal models that predictably result in isolated microtia, the abnormal processes are not yet understood well enough to control them. Future work should focus on treatment strategies for microtia in animal models that can eventually be translated to humans linked to the genetic processes controlling gene expression and molecular transcription factors.

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C. elaboration of figures and tables:	50%	50%
D. drafting, reviewing and writing of the text:	50%	50%
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