



TEXAS

Department of State Health Services
Birth Defects Epidemiology and Surveillance

BIRTH DEFECT RISK FACTOR SERIES: MICROTIA AND ANOTIA

DEFINITION

The ear is composed of three parts: the internal, middle, and external portions. Microtia is a condition in which the external portion of the ear (the auricle) is malformed. In the strictest definition, there is also narrowing or absence of the external auditory canal (external auditory meatus). This is different from a "small ear" in which the ear is normally shaped, but smaller than normal as in Down syndrome. Microtia varies in severity from barely discernable to an external ear with major structural changes. Anotia is the total absence of the auricle most often with narrowing or absence of the external auditory meatus. Anotia/microtia can occur unilaterally or bilaterally.

Microtia and anotia can be grouped into four types according to the level of affliction (Meurman 1957):

Type I: The external ear is small and the auricle retains most of its normal structure. The external auditory meatus is usually present.

Type II: The external ear is moderately anomalous. The auricle can be hook-, S-, or question mark shaped in appearance.

Type III: The external is a rudimentary soft tissue structure with no cartilage; the auricle does not have a normal appearance.

Type IV: Anotia; all external ear structures are absent.

Cases of microtia may be difficult to define. The term microtia may be assigned to various anomalous conditions of the ears; type I microtia may be excluded from certain analyses due to the minimal change of the ear (Harris 1996).

Approximately 29% of the cases of diagnosed microtia do not have full atresia of the external auditory meatus (Castillo 1986). Cases of isolated atresia or stenosis of the external auditory canal are generally excluded from the diagnosis of microtia/anotia. Anotia accounts for 13-22% of the cases of microtia and anotia combined (Harris 1996, Mastroiacovo 1995).

Anotia/microtia is an isolated condition in 65% of cases (Harris 1996, Mastroiacovo 1995, Castillo 1986), although several investigations reported isolated rates of less than 50% (Sanchez 1997, Castillo 1990). One investigation reported no difference between microtia and anotia in the proportion of isolated cases (Harris 1996). Preauricular skin tags are often present in microtia types I-III. Inner ear anomalies are present in 12-50% of cases of microtia or anotia (Buyse 1990). Over 80% of the cases of microtia or anotia are unilateral (Sanchez 1997, Mastroiacovo 1995). Of the unilateral cases of microtia or anotia, approximately 60% occur on the right side (Paulozzi 1999, Sanchez 1997, Harris 1996, Mastroiacovo 1995).

Anotia/microtia can occur independently or as part of a syndrome. One of the syndromes associated with anotia and microtia is First Arch Syndrome, which consists of congenital anomalies of the eyes, ears, palate, and mandible (Moore 1998). Anotia/microtia is also associated with

Oculo-auriculo-vertebral spectrum (OAV), which also involves facial, renal, and vertebral anomalies (Beck 2005, Bonilla 2005, Llano-Rivas 1999). Goldenhar syndrome is the most severe manifestation of OAV. The most common phenotype associated with microtia or anotia is hemifacial microsomia, occurring in 14% of cases (Carey 1993). Other multiple congenital anomaly complexes associated with microtia or anotia include Treacher-Collins, Nager, and CHARGE syndromes, among others (Forrester 2005, Sanchez 1997, Harris 1996, Carey 1993).

Chromosomal abnormalities occur in 6-16% of cases of microtia or anotia (Sanchez 1997, Harris 1996). Chromosomal abnormalities associated with microtia or anotia include trisomy 21, trisomy 18, trisomy 13, and the deletion complexes 18q-, 18p-, and 5p- (Harris 1996, Carey 1993, Buyse 1990). Autosomal dominant inheritance of microtia or anotia has been reported in some families (Buyse 1990).

Other birth defects associated with microtia/anotia include holoprosencephaly, facial clefts, cardiac defects, anophthalmia/microphthalmia, esophageal atresia, limb reduction deformities, renal anomalies, polydactyly, and vertebral anomalies (Wang 2001, Harris 1996, Mastroiacovo 1995). Some of these associations are based on a common etiology. For example, holoprosencephaly and microtia are both commonly found in trisomy 13.

EMBRYOLOGY

The ear is composed of three parts, and each of these parts has a slightly different developmental process (Riley 2005). The external portion of the ear is composed of the auricle, the external auditory meatus, and the external layer of the eardrum (Moore 1998). The most visible portion of the ear is the auricle. It is formed by a series of auricular hillocks that surround the first pharyngeal groove during the sixth week of gestation (Bonilla 2005, Moore 1998). Initially, the auricle forms at the base of the neck, but as the mandible develops, the auricles migrate to their normal anatomical position (Moore 1998). Microtia or anotia occurs when the tissues that form the auricle fail to develop.

ETIOLOGY

The cause of isolated or non-syndromic anotia/microtia is not known, however it is believed that there is a genetic component involved (Bonilla 2005).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

One investigation reported no association between race/ethnicity and microtia (Castillo 1986). However, others have found the rate per 10,000 births of microtia and anotia to be higher in Hispanics and Asians, than in whites and blacks (Forrester 2005, Shaw 2004, Harris 1996). A New Mexico-based study observed increased risk of microtia in Native Americans (Aase 1977). Children of mixed Hispanic-white race/ethnicity have been found to have higher rates of microtia compared to children of both white, non-Hispanic parents (Yang 2004).

Although one investigation reported no association between sex and nonsyndromic anotia and microtia (Mastroiacovo 1995), other studies observed a preponderance of this defect among males (Shaw 2004, Sanchez 1997, Harris 1996). In one study, the sex ratio was higher in infants with isolated microtia/anotia (1.66) than in infants with microtia/anotia in conjunction with other birth defects (1.24) (Harris 1996).

No secular trends have been reported for microtia/anotia (Sanchez 1997, Mastroiacovo 1995). Additionally, one investigation reported no monthly or seasonal variations for microtia (Castilla et al., 1990).

There does not appear to be an association between maternal age and risk of microtia/anotia (Mastroiacovo 1995, Castillo 1986). One investigation reported increased risk of nonchromosomal microtia/anotia with increasing maternal age; however, the authors suggested this association might be due to undiagnosed trisomies among the cases (Harris 1996). One study found no association between nonsyndromic microtia and anotia and paternal age (Mastroiacovo 1995) while another study reported increased risk of microtia with elevated paternal age in an area with a high rate of microtia (Castillo 1986).

The relationship between anotia/microtia and parity is unclear (Shaw 2004). While some studies have shown that the risk for these defects is elevated in primiparous women, others have shown the reverse, with the risk increased among women with higher parity (Mastroiacovo 1995, Harris 1996). No association between microtia and multiple gestation pregnancy (Mastroiacovo 1995, Castillo 1986) has been identified. However, the relationship between consanguinity and anotia/microtia is ambiguous (Mastroiacovo 1995). It is also unclear if having an affected family member is a risk factor; however, it is suspected that this defect is subject to multifactorial inheritance (Mastroiacovo 1995).

Microtia or anotia risk is elevated with lower birth weight (Mastroiacovo 1995, Castillo 1986) but does not appear associated with large for gestational age (Lapunzina 2002). While one investigation observed no association between microtia and gestational age (Castillo 1986), another investigation identified increased risk of nonsyndromic microtia and anotia with lower gestational age among those cases with associated birth defects (Mastroiacovo 1995).

FACTORS IN LIFESTYLE OR ENVIRONMENT

Several studies in South America have found increased risk of microtia/anotia at higher elevations (Castilla 1999, Lopez-Camelo 1996, Castilla 1986). One potential explanation offered for this observation is hypoxia (during the embryonic period).

Maternal and paternal education levels were not associated with risk of microtia or anotia (Mastroiacovo 1995, Castillo 1986). A study in Argentina observed an increased adjusted rate ratio of 1.88 for microtia in counties with cement, lime, and plaster industry (Castillo 2000).

Microtia/anotia has been associated with in utero exposure to thalidomide (Carey 1993, Buyse 1990) and isotretinoin (Accutaine™) (Lynberg 1990, Jahn 1987). One study reported increased risk of vascular disruption spectrum defects such as microtia and first trimester use of misoprostol, an orally active prostaglandin (Vargas 2000). While a relationship between maternal smoking during first trimester and nonsyndromic microtia/anotia has been observed (Mastroiacovo 1995), one study indicated that paternal smoking is also a risk factor for anotia and microtia (Zhang 1992).

Maternal insulin-dependent diabetes has been suggested as risk factor for anotia/microtia (Shaw 2004, Ewart-Toland 2000). One study reported no association between microtia and maternal acute illness or vaginal bleeding (Castillo 1986) while another study observed a negative association between acute maternal disease and microtia (Lopez-Camelo 1996). Microtia has been associated with maternal influenza (Lopez-Camelo 1996), and microtia/anotia has been reported among infants born to mothers with rubella or intrauterine infection (Buyse, 1990).

PREVALENCE

The anotia/microtia birth prevalence in Texas among 1999-2003 deliveries was 2.82 cases per 10,000 live births (Texas Department of State Health Services 2006). Birth prevalence in the United States ranges from 0.22-10.28 per 10,000 live births (National Center on Birth Defects and Developmental Disabilities 2006). Differences in prevalence may be due to differences in case inclusion criteria.

REFERENCES

- Aase JM, Tegtmeier RE. Microtia in New Mexico: evidence for multifactorial causation. *Birth Defects Orig Artic Ser* 1977;13:113-116.
- Beck AE, Hudgins L, Hoyme HE. Autosomal dominant microtia and ocular coloboma: new syndrome or an extension of the oculo-auriculo-vertebral spectrum? *American Journal of Medical Genetics* 2005; 134A:359-362.
- Bonilla JA. Microtia. <http://www.emedicine.com/ped/topic3003.htm>. Updated August 26, 2004. Accessed September 13, 2005.
- Buyse ME, ed. Ear, Microtia-Atresia. In: *Birth Defects Encyclopedia*. Cambridge, Massachusetts: Blackwell Scientific Publications, 1990:591-592.
- Carey JC. External ear. In: Stevenson RE, Hall JG, Goodman RM, eds. *Human Malformations and Related Anomalies*. New York: Oxford University Press 1993:193-219.
- Castilla EE, Campana H, Camelo JS. Economic activity and congenital anomalies: an ecologic study in Argentina. *Environ Health Perspect* 2000;108:193-197.
- Castilla EE, Lopez-Camelo JS, Campana H. Altitude as a risk factor for congenital anomalies. *Am J Med Genet* 1999;86:9-14.
- Castilla EE, Orioli IM, Lugarinho R, Dutra GP, Lopez-Camelo JS, Campana HE, Spagnolo A, Mastroiacovo P. Monthly and seasonal variations in the frequency of congenital anomalies. *Int J Epidemiol* 1990;19:399-404.
- Castilla EE, Lopez-Camelo JS. The surveillance of birth defects in South America. In: *Advances in Mutagenesis Research*. New York: Springer-Verlag 1990:191-210.
- Castilla EE, Orioli IM. Prevalence rates of microtia in South America. *Int J Epidemiol* 1986;15:364-368.
- Crane JP, Beaver HA. Midtrimester sonographic diagnosis of mandibulofacial dysostosis. *Am J Med Genet* 1986;25:251-255.
- Ewart-Toland A, Yankowitz J, Winder A, Imagine R, Cox VA, Aylsworth AS, Golabi M. Oculo-auriculo-vertebral abnormalities in children of diabetic mothers. *Am J Med Genet* 2000;90:303-309.
- Forrester MB, Merz RD. Congenit Anom (Kyoto). Descriptive epidemiology of anotia and microtia, Hawaii, 1986-2002. 2005 Dec;45(4):119- 24.
- Harris J, Kallen B, Robert E. The epidemiology of anotia and microtia. *J Med Genet* 1996;33:809-813.
- Jahn AF, Ganti K. Major auricular malformations due to accutane (isotretinoin). *Laryngoscope* 1997;97:832-835.
- Lapunzina P, Lopez Camelo JS, Rittler M, Castilla EE. Risks of congenital anomalies in large for gestational age infants. *J Pediatr* 2002;140:200-204.
- Llano-Rivas I, Gonzalez-de Angel A, del Castillo V, Reyes R, Carnevale A. Microtia: a clinical and genetic study at the National Institute of Pediatrics in Mexico City. *Archives of medical research* 1999;30:120-124.
- Lopez-Camelo JS, Orioli IM. Heterogeneous rates for birth defects in Latin America: hints on causality. *Genet Epidemiol* 1996;13:469-481.
- Lynberg MC, Khoury MJ, Lammer EJ, Waller KO, Cordero JF, Erickson JD. Sensitivity, specificity, and positive predictive value of multiple malformations in isotretinoin embryopathy surveillance. *Teratology* 1990;42:513-519.
- Mastroiacovo P, Corchia C, Botto LD, Lanni R, Zampino G, Fusco D. Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. *J Med Genet* 1995;32:453-457.
- Meurman Y. Congenital microtia and meatal atresia. *Arch Otolaryngol* 1957;66:443.

- National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Birth defects surveillance data from selected states, 1999-2003. Birth Defects Res A Clin Mol Teratol. 2006 Dec;76(12):894-960.
- Paulozzi LJ, Lary JM. Laterality patterns in infants with external birth defects. Teratology 1999;60:265-271.
- Riley BB, Phillips BT. Ringing in the new ear: resolution of cell interactions in otic development. Developmental Biology 2003;261:289-312.
- Rittler M, Liascovich R, Lopez-Camelo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. Am J Med Genet 2001;102:36-43.
- Sanchez O, Mendez, Gomez E, Guerra D. Clinico-epidemiologic study of microtia]. Invest Clin 1997;38:203-217.
- Shaw GM, Carmichael SL, Kaidarova Z, Haris JA. Epidemiologic characteristics of anotia and microtia in California, 1989-1997. Birth Defects Research (Part A) 2004;70:472-475.
- Texas Department of State Health Services. Texas birth defects registry report of birth defects among 1999-2003 deliveries. 2006.
- Vargas FR, Schuler-Faccini L, Brunoni D, Kim C, Meloni VF, Sugayama SM, Albano L, Llerena JC, Almeida JC, Duarte A, Cavalcanti DP, Goloni-Bertollo E, Conte A, Koren G, Addis A. Prenatal exposure to misoprostol and vascular disruption defects: a case-control study. Am J Med Genet 2000;95:302-306.
- Wang RY, Early DL, Ruder RO, Graham JM. Syndromic ear anomalies and renal ultrasounds. Pediatrics 2001;108:2.
- Yang J, Carmichael SL, Kaidarova Z, Shaw GM. Risks of selected congenital malformations among offspring of mixed race-ethnicity. Birth Defects Res A Clin Mol Teratol. 2004 Oct;70(10):820-4.

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*