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Epidemiology and risk factors for microtia in Colombia

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Abstract
Introduction and objectives: Microtia is a major malformation of the auricle, comprising a clinical spectrum ranging from a slight reduction in the size of the auricle or one of its parts to the complete absence of the pinna (anotia). Its prevalence varies according to the region of the world it is evaluated in. We analyzed a range of maternal, neonatal, and familial variables in a case group and a control group, and compared them with the existing literature.
Methods: We collected information from the Latin-American Collaborative Study on Congenital Malformations (ECLAMC) gathered between 2001 and 2006, where we found 27 cases of isolated microtia; we also collected information from 103 control subjects. Data were analyzed using Student *t* test and odds ratio (OR).
Results: Microtia distribution was 3 (11.1%) patients with grade I microtia, 19 (70.4%) with grade II microtia, 2 (7.4%) with grade III microtia. We found no patients with anotia. Regarding laterality, the right side was involved more often. Male-to-female ratio was 1.7:1. Birth weight ≤2500 g produces an OR of 3.25 (95%CI, 1.11-9.58) for the development of microtia.
Conclusions: Microtia may be directly or indirectly associated with the early onset of labour. Future studies should include long-term follow up of the patients in order to detect possible anomalies of the oculo-auriculo-vertebral spectrum. It is also important to take anthropometric measurements to increase the likelihood of detecting cases of grade I microtia and mid-face hypoplasia, and to define with greater accuracy whether isolated microtia is the mildest form of the oculo-auriculo-vertebral syndrome.

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PALABRAS CLAVE
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ECLAMC

Epidemiología y factores de riesgo para microtia en Colombia

Resumen
Introducción y objetivos: Microtia es una malformación mayor del pabellón auricular que presenta un espectro que va desde la disminución leve del tamaño del pabellón o una de sus partes hasta la ausencia total del pabellón (anotia). Su prevalencia varía según la región del mundo en la cual se evalúe. Analizamos diferentes variables maternas, neonatales y familiares, entre casos y controles, en comparación con las de la literatura existente.
Métodos: Recolectamos información del Estudio Colaborativo Latinoamericano de Malformaciones Congénitas registrada en 2001-2006; encontramos 27 casos de microtia aislada, también recabamos información de 103 controles. Analizamos la información mediante la prueba de la t de Student y la *odds ratio* (OR).
Resultados: La distribución de la microtia fue: 3 (11,1%) pacientes con microtia I, 19 (70,4%) con microtia II y 2 (7,4%) con microtia III. No había pacientes con anotia. La lateralidad más común fue el lado derecho. La proporción varones/mujeres fue de 1,7:1. Tener un peso al nacer ≤ 2.500 g genera una OR de 3,25 (intervalo de confianza del 95%, 1,11-9,58) para el desarrollo de microtia.
Conclusiones: La microtia puede tener relación directa o indirecta con la precipitación del inicio en el trabajo de parto. En futuros estudios los pacientes deberían tener un seguimiento a largo plazo para detectar posibles anomalías del espectro oculoauriculovertebral. También es importante realizar medidas antropométricas para aumentar la probabilidad de detección en casos de microtia de grado I e hipoplasia facial media y definir con mayor exactitud si la microtia aislada es la forma más leve del espectro oculoauriculovertebral.

Introduction

Microtia is a major malformation of the ear which presents a spectrum ranging from a mild reduction in the size of the ear or one of its parts to the total absence of the ear (anotia). It occurs predominantly on the right side.[1-6] Its prevalence varies by region in which it is evaluated. In Hawaii, the prevalence is of 3.79/10 000 live births[2]; in France it is 0.83; in Sweden 2.35; in California 2; in China 1.4; in Venezuela 3.8; and in the Latin American Collaborative Study of Congenital Malformations (ECLAMC),[7] 3.7. The prevalence increases in ethnic groups, such as among Japanese, Hispanic, and Native American Indian populations.[4,8,9]

Microtia can occur in isolation or as part of several syndromes, such as embryopathies due to isotretinoin, alcohol, thalidomide, and maternal diabetes, it can also be found in Treacher-Collins syndrome and as part of the oculo-auriculo-vertebral spectrum (also known as Goldenhar syndrome or hemifacial microsomia).[10-13] In addition to the external ear, microtia may affect the middle ear and cause hearing alterations which in 80%-90% of cases present as conductive hypoacusis; in a minority, it may be present as sensorineural or mixed hearing loss.[8,13,14] The importance of the above is that hearing loss hinders cognitive development of children, so its early detection and correction will improve the prognosis and development.[15] There are currently devices such as BAHA™ which are useful in the treatment of conductive hearing loss caused by abnormalities in the middle ear; these devices are attached to the bone and function through vibrations transmitted to the cochlea by the cranial bones without passing through the middle ear.[16]

Altitude above sea level is related to the development of microtia,[17] another important aspect is gender, as it has been proven to have a greater prevalence in men,[1,2,4,18] although there are isolated studies that report a greater prevalence in women.[19] Variables such as maternal age and number of gestations present marked trends in favour of developing microtia. Women over 35 years are 1.47 times (95% confidence interval [CI], 1.16-1.87) more likely to have children with some degree of microtia, together with mothers who have had 4 or more pregnancies, with 1.17 times greater risk (95%CI, 1.03-1.33).[1,4,8,20]

All these factors have some influence in the embryological development of the ear, which occurs between the fifth and ninth weeks of gestation; the processes under way in this period are a source of many debates. The existing theory proposes the formation of 6 His mounds or promontories and that each of them gives rise to different parts of the ear. Some authors consider that the fusion and consolidation process of the ear is more complex than indicated above.[1,4,5] For this reason, the starting point triggering an ear with microtia is not exactly known.

Since even the embryological development and its alterations have not been clearly defined,[1,8,21-25] we decided to carried out a study to analyze different maternal, neonatal, and familiar variables which may directly or indirectly influence the embryogenesis of the ear and compare these with data in the literature.

Materials and methods

The Institute of Human Genetics, at the Pontifical Xavierian University, Bogotá, Colombia, has participated in the ECLAMC project since 2001.[7] We obtained data from all babies born alive or stillborn, weighing ≥500 g, who presented major or minor congenital malformations. Additionally, for each

case of malformation data was collected on the next healthy live newborn of the same gender. We included 6 hospitals: 4 located in the city of Bogotá, the country's capital, 1 in the city of Manizales, Caldas Department (5°3'43" N, 75°29'43" W) and 1 in the Ubaté municipality, Cundinamarca department (5°18'22" N, 73°48'55" W). The period analyzed was between 2001 and 2006.

We included all patients diagnosed with non-syndromic microtia, and excluded patients with microtia associated with one or more major malformations found in other organs.[8,26] We considered as grade I microtia an alteration in size, but with recognition of all its parts; grade II microtia: abnormal ear, with some identifiable anatomical malformations; grade III microtia: major deformity of the ear, without clearly identifiable parts with the presence of an auricular appendix of variable size and shape, and finally anotia: total absence of the ear. We evaluated the laterality of malformations classifying them as right, left, and bilateral. The variables analyzed as potential risk factors were: maternal age, parity, gestational age, birth weight, maternal signs and symptoms, acute and chronic maternal disease, physical factors (injuries, exposure to radiation or chemicals), habit of smoking, drinking or taking drugs during pregnancy, use of medications during pregnancy, birth presentation, history of miscarriages, and high-risk pregnancy.[27]

Data analysis

Quantitative variables were compared with Student *t* statistical test with a confidence value of 95%. Qualitative variables were compared using the odds ratio (OR) with a confidence interval of 95%.

Results

Between 2001 and 2006, we found 29 cases of microtia; 2 cases were excluded due to other concomitant malformations, ie, we deemed the microtias to be related to syndromic alterations, leaving 27 cases of isolated microtia. The prevalence found by ECLAMC in Colombia is 6.4/10 000 live births. Furthermore, data were collected from 103 control subjects, to obtain a case:control ratio of 1:3.8. Five cases were collected at the David Restrepo Clinic, 3 cases in the Emmanuel Clinic, 2 cases at the Hospital "El Salvador" in Ubaté, 10 cases at the Hospital Universitario "San Ignacio," and 7 cases in the Hospital de Manizales.

Of the 27 microtias, 5 (18%) presented concomitant pre-auricular appendix and 1 case (3%) presented microtia with appendix and pre-auricular fossa. There were 3 patients (11.1%) with grade I microtia, 19 (70.4%) with grade II microtia, 2 (7.4%) with grade III microtia, and 3 (11.1%) were unclassified. There were no patients with anotia. In terms of laterality, in our study there was a higher prevalence of the right side, with 17 (62.9%) cases; the left side with 6 (22.2%) cases, and 2 (7.4%) cases were bilateral. We were unable to obtain information about the laterality in 2 (7.4%) cases. Males were more frequently affected than women, with a ratio of 1.7:1.

The analysis and description of the quantitative and qualitative variables can be found in Tables 1 and 2 respectively. In addition to this analysis, we compared the birth weight between cases and controls; we found that 6 cases (22.2%) and 9 controls (8.7%) had a weight <2500 g (OR=3.25; 95%CI, 1.11-9.58).

Table 1 Comparison of quantitative variables between cases (n=27) and control subjects (n=103) (95%confidence level).

Variable	Cases, average (SD)	Controls, average (SD)	*P*
Weight at birth, g	2777.03 (677.52)	3052 (473.21)	NS
Maternal age	25.48 (5.67)	26.2 (6.73)	NS
Parity	2.22 (1.09)	2.22 (1.37)	NS
Gestational age	37.51 (2.56)	38.76 (2.09)	.009

NS indicates no statistical significance; SD, standard deviation.

Discussion

The distribution of microtia according to phenotypic classification shows a predominance of grade II microtia (79.2% of cases where we obtained a description). The absence of anotias is remarkable, as well as the low number of grade I microtias which could be due to under-diagnosis, as the evaluators may consider these ears as normal. Compared to a work carried out in Italy,[19] where isolated grade 2 microtia was the sum of our grade II and III microtias, we observed a difference in this distribution because in the Italian sample 55.3%were placed in category 2, whereas in our population it was 87.5%.

In our study we found that most cases of non-syndromic microtia are on the right side and the minority of cases, bilateral, this is consistent with findings in different regions of the world.[1-6,8,18,20-22,28] In analyzing the gender variable, we find that the results obtained are consistent with those described in the world literature, which shows a higher prevalence in males.[1,2,10,18,20,21,29]

Birth weight ≤2500 g resulted in an increased frequency of microtia, consistent with the data published so far.[2,19] When we analyzed and compared the average weight for cases and controls, we observed no significant differences. Maternal age did not present differences between cases and controls, but in the literature we have observed differences in women over 35 years of age.[2,4,20] When comparing maternal parity, no differences were found, this disagrees with the reports from the literature where it is considered that parity greater than 4 children is related to the development of this anomaly.[1,8,19,20]

The gestational age was significantly lower among our cases, which agrees with the findings of a study conducted in Hawaii, United States.[2] This fact has been linked to other major malformations,[2,19,30] indicating that defects have a direct or indirect effect on precipitating the onset of childbirth. We found no relationship between microtia and consumption of medicinal drugs during pregnancy; when we studied the consumption of folic acid during pregnancy, we found no differences, thus enabling us to see that microtia evaluated in our series does not seem to be related to a

Table 2 Comparison of qualitative variables between cases (n=27) and control subjects (n=103)

Variable	Cases		Controls		OR (95%CI)
	Yes	No	Yes	No	
Drug use during pregnancy	22	5	84	19	1 (0.33-2.96)
Ferrous sulphate	7	20	35	68	0.68 (0.26–1.76)
Folic acid	8	19	22	81	1.55 (0.6–4.01)
Ampicillin	5	22	19	84	1 (0.34–2.99)
Metronidazole ovules	4	23	18	85	0.82 (0.25–2.67)
Calcium	5	22	15	88	1.33 (0.4–4.07)
Acute disease during pregnancy	16	11	74	29	0.57 (0.24–1.37)
Vaginosis	6	21	24	79	0.94 (0.34–2.6)
Urinary tract infection	3	24	25	78	0.39 (0.11–1.41)
Viral rhinopharyngitis	3	24	6	97	2.02 (0.47–8.67)
Preeclampsia	1	26	3	100	1.28 (0.13–12.84)
Chronic disease during pregnancy	2	25	13	90	0.55 (0.12-2.62)
Signs and symptoms during pregnancy	16	11	39	64	2.39 (1.01-5.67)[a]
Nausea	11	16	25	78	2.15 (0.88-5.22)
Vomiting	5	22	20	83	0.94 (0.32-2.8)
Cephalalgia	6	21	17	86	1.45 (0.51-4.11)
Epigastralgia	3	24	2	101	6.31 (1.39-9)[a]
Pyrosis	2	25	2	101	4.04 (0.54-30.1)
Family history of malformation	7	20	11	92	2.93 (1.01-8.48)[a]
Risk factor during pregnancy	6	21	14	89	1.82 (0.62-5.29)
Multiple pregnancy	1	26	1	102	3.92 (0.24-64.84)
Metrorrhagia	4	23	16	87	0.95 (0.29-3.1)
Cephalic presentation	26	1	98	5	1.33 (0.15-11.85)
Miscarriages	3	24	18	85	0.59 (0.16-2.17)
Smoking during pregnancy[b]	1	26	8	87	0.42 (0.05-3.5)
Consumption of alcohol during pregnancy[b]	2	25	3	92	2.45 (0.39-15.49)
Use of illicit drugs during pregnancy	0	27	0	103	N/A

CI indicates confidence interval; OR, odds ratio.
[a]Statistically significant difference.
[b]No information was obtained about the consumption of alcohol and tobacco during pregnancy in 8 control subjects.

lack of this nutrient.[31] The literature does not describe any connection between acute or chronic disease and the development of microtia. When we investigated this variable, we found no statistically significant difference which enabled us to establish a relationship. Moreover, we believe that data regarding consumption of alcohol, tobacco, and illicit drugs are probably under-registered due to the social burden that their use entails; due to this we cannot accurately determine whether microtia is related to these factors.

Currently, the presentation of microtia unrelated to other malformations is not considered an isolated event, but as the mildest form of presentation of the oculo-auriculo-vertebral spectrum. In our study, we believe that a significant proportion of cases may be related to this spectrum, due to lack of monitoring and lack of measurement of anthropometric parameters that allow us to detect other concomitant anomalies, such as facial asymmetry, decreased size of the hemiface, hypoplasia of the facial, malar, maxillar or mandibular musculature, hearing loss, pre-auricular appendages and fossae, macrostomy, Fallot tetralogy, coarctation of the aorta, pulmonary hypoplasia, ectopic kidney, renal agenesis, vertebral abnormalities, ocular abnormalities, or central nervous system defects.[32] Six of the 27 microtia cases presented concomitantly pre-auricular fossa or appendage; it is likely that these cases are not isolated microtia, but part of the oculo-auriculo-vertebral spectrum.

Conclusions

We consider that future studies in patients with microtia should have a long-term monitoring to detect any anomalies that may be part of the oculo-auriculo-vertebral spectrum. Due to the co-morbidity with hearing disorders, we propose a hearing screening and evaluation of the anatomical structures of middle and internal ear through diagnostic imaging in patients with diagnosis of microtia. It is also important to perform anthropometric measurements to

increase sensitivity of detection in cases of grade I microtia and medial facial hypoplasia and thus more accurately determine whether or not isolated microtia is the mildest form of the oculo-auriculo-vertebral spectrum.

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Conflict of interests

The authors have indicated there is no conflict of interest.

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