BRIEF COMMUNICATION

Clinical Features of 149 Patients With Facio-auriculo-vertebral Spectrum

Liliana A. Muñoz-Pedroza, a María L. Arenas-Sordo b,∗

a Servicio de Genética, Asociación Leonesa de Distrofia Muscular S.A. León, Guanajuato, Mexico
b Servicio de Genética, Instituto Nacional de Rehabilitación, Mexico City, Mexico

Received 4 January 2013; accepted 27 March 2013

KEYWORDS
Facio-auriculo-vertebral sequence; Microtia; Hemifacial microsomia; Goldenhar syndrome

Abstract  Facio-auriculo-vertebral (FAV) spectrum, also known as Goldenhar syndrome or first and second branchial arch syndrome, is a complex of mainly craniofacial and vertebral anomalies. Microtia is a principal malformation in this complex; it can be unilateral or bilateral.

We performed an observational, retrospective, transverse descriptive clinical study, reviewing 149 records of patients with a diagnosis of microtia treated in the Genetics Department.

There was no significant difference in the sex of the individuals involved. The mean age was 6.97 years, with a range of 1-52 years. We founded a positive inbreeding in 14 patients and consanguinity in 1 case. There was a family history of microtia in 37 cases. The most frequent malformations, besides microtia, were facial, costo-vertebral, limb, cardiac, genital, eye and other defects.

Patients had a high percentage of family history, which could suggest an autosomal dominant inheritance with reduced penetrance.

© 2013 Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE
Espectro facio-aurículo-vertebral; Microtia; Microsomia hemifacial; Goldenhar

Resumen  El espectro facio-aurículo-vertebral, también denominado síndrome de Goldenhar, o síndrome del primer y segundo arcos branquiales, es un complejo de anomalías craneofaciales y vertebrales principalmente. La malformación eje de este complejo es la microtia, unilateral o bilateral.

Se realizó una investigación clínica observacional, retrospectiva trasversal y descriptiva, revisando 149 expedientes de pacientes con diagnóstico de microtia.

Please cite this article as: Muñoz-Pedroza LA, Arenas-Sordo ML. Manifestaciones clínicas de 149 pacientes con espectro facio-auriculo-vertebral. Acta Otorrinolaringol Esp. 2013;64:359-362.

* Corresponding author.
E-mail addresses: mlarenassordo@hotmail.com, marenas@inr.gob.mx, asgk@unam.mx (M.L. Arenas-Sordo).

2173-5735/$ – see front matter © 2013 Elsevier España, S.L. All rights reserved.
Introduction

Facio-auriculo-vertebral (HAV) spectrum, also called Goldenhar syndrome or syndrome of first and second brachial arches, is a complex of mainly craniofacial and vertebral anomalies. It was originally described by von Arlt, but it remained unconsidered until 1952, when Goldenhar reported 3 new cases of this complex, which was then referred to with his name.1

In 1990, Gorlin et al.2 extended the specifications to a complex that included a FAV syndrome, with hemifacial microsomia, otomandibular dysostosis, as well as Goldenhar syndrome and other anomalies of the first and second brachial arches. The central malformation of this complex is the microtia, and it can even be the sole feature. However, it is normally found in association with mandibular hypoplasia, vertebral malformations and other systemic features.3

Microtia is a malformation characterised by the absence of some parts of the ear or of the entire ear. It can include the external auditory canal and can be unilateral or bilateral.4

Its incidence varies according to region and is considered to range from 1:500 to 1:3000 live births (LBS). In Mexico the incidence has been reported as 1:1500 LBS. It is more frequent in males, with a ratio of 2:1.1

The different structures developed in the auditory system of vertebrate animals come about from the developed of the 6 pharyngeal arches during embryogenesis. The development of the middle ear requires a series of interactions between the epithelium and mesenchyme. The small bones of the middle ear derive from the mesenchyme of neural crest cells.3 Experiments with inactivation of genes has identified some that are necessary for the formation of middle ear components, such as endothelin-1 (ET-1) and the fibroblast growth factor 8 (FGF-8), which probably mediate in epithelial-mesenchymal interactions; other genes (Eya1, Prx1, Hoxa1, Hoxa2, Dlx1, Dlx2, Dlx5 and Gsc) have been implicated in the processes of modelling and morphogenesis of the mesenchymal derivatives.5-10 The genetic expression of Tbx1 plays a key role in the formation of the middle and outer ear in mice. Mutant mice homozygous for Tbx1 have defects in the development of the middle and outer ear. This gene also plays a significant role in the formation of the otic vesicle, as has been seen in knock-out mice, in which there is a failure in the formation of sensory organs of the inner ear of the mice. This gene is probably necessary for the development of sensory organs and for the suppression of the determination of the fate of the neuronal cells in the otic vesicle.9

Methods

We performed a retrospective, transversal and descriptive observational clinical research study, reviewing 149 case files of patients diagnosed with microtia.

The following data were collected: age, sex, origin, consanguinity, inbreeding, heredofamilial history, number of relatives having microtia, prenatal history, language and intellectual development, type of microtia according to the Weerd classification, and the presence of associated malformations.

Results

In the total of 149 patients, 60% came from the Mexican Federal District (FD) and 28% from the state of Mexico, while the rest (12%) came from states near the FD. Mean age was 6.97 years, ranging from 1 to 52 with a median of 6.

The patients were female in 52.35% of the cases, and male in 47.65%.

As antecedents we found that 14 patients reported positive inbreeding, consanguinity in only 1 case and family history of microtia in 37 patients (24.83%). Of the microtia cases, some were in first-degree relatives, but there were also cases of second- and third-degree. Most had only 1 relative affected, but there were some that had even up to 4 (Table 1).

Of the total of patients, 67 had no perinatal history. The rest presented history of medicine intake (14), infection of the upper airways (16), urinary and/or vaginal infection (21), threat of miscarriage (36), twin pregnancy (4) and maternal disease (17); epilepsy, diabetes mellitus (DM) (2), pre-eclampsia and alcoholism.

<table>
<thead>
<tr>
<th>Number of relatives</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>16.2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 2  Genes Studied That Have Been Implicated in Ear Formation.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Activity</th>
<th>OMIM No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGR-8</td>
<td>10q24.32</td>
<td>Fibroblast growth receptor 8</td>
<td>OMIM 600483</td>
</tr>
<tr>
<td>Eya1</td>
<td>8q13.3</td>
<td>Protein phosphatase</td>
<td>OMIM 601653</td>
</tr>
<tr>
<td>Prx1</td>
<td>Yq11.223</td>
<td>Tyrosine phosphatase</td>
<td>OMIM 167420</td>
</tr>
<tr>
<td>Hoxa1</td>
<td>7p15.2</td>
<td>Transcription factor</td>
<td>OMIM 142955</td>
</tr>
<tr>
<td>Hoxa2</td>
<td>7p15.2</td>
<td>Transcription factor</td>
<td>OMIM 604685</td>
</tr>
<tr>
<td>Dlx1</td>
<td>2q31.1</td>
<td>Transcription factor</td>
<td>OMIM 600029</td>
</tr>
<tr>
<td>Dlx2</td>
<td>2q31.1</td>
<td>Transcription factor</td>
<td>OMIM 138890</td>
</tr>
<tr>
<td>Dlx5</td>
<td>7q21.3</td>
<td>Transcription factor</td>
<td>OMIM 600028</td>
</tr>
<tr>
<td>Gsc</td>
<td>1q43.21</td>
<td>Transcription factor</td>
<td>OMIM 138890</td>
</tr>
<tr>
<td>Tbx1</td>
<td>22q11.21</td>
<td>Transcription factor</td>
<td>OMIM 602054</td>
</tr>
<tr>
<td>Six2</td>
<td>2p21</td>
<td>Transcription factor</td>
<td>OMIM 604994</td>
</tr>
</tbody>
</table>

Microtia was bilateral in 51 cases (34%) and unilateral in 98 (65.7%). Of the unilateral cases, 76 were of the right side and 22, the left. Nearly 70% of the patients presented grade ii or iii microtia/atresia in a single ear or in both.

The patients that presented only microtia as a feature were 92 (61.74%). Those with associated malformations were 57 (38.25%); the impairments were grouped into the following: facial, costovertebral, limb, cardiac, genital, ophthalmological and others.

Within craniofacial malformation we found: microcephaly, facial asymmetry, cleft palate, submucosal cleft palate, cleft lip and palate, facial paralysis, palpebral ptosis and capillary haemangioma in the skin of the occipital area.

The costovertebral malformations found consisted of wedge vertebra, butterfly vertebra, hemivertebra and costal fusion.

In the urinary system the malformations were: renal hypoplasia, renal agenesis, renal cyst, lobulated bladder, megareter and double-collector system. Genital malformations found were hypospadias and cryptorchidism.

In the limbs, malformations presented were polydactyly and camptodactyly. Ophthalmological malformations were microphthalmia and coloboma of the eyelid.

With respect to cardiac malformations, we found intra-atrial communication and aneurism of the intra-atrial septum.

In addition, 1 patient presented imperforate anus and another patient, spastic hemiparesis.

Appropriate intellectual and language development was presented by 75% of the patients, 16.8% presented language delay, and 8.2% showed intellectual disability.

Discussion

The pathology of FAV spectrum is a complex clinical entity in which there is probably genetic heterogeneity. Multiple associated malformations have been described in it.

In our study population, the sexes were balanced, although with a slightly higher female rate. This is in contrast to what has been described in other articles, including one on Mexican patients. There is probably a population bias involved whose origin is still unknown.

Various prenatal factors have been identified as factors of risk, including multiple pregnancies, anaemia, advanced maternal age, threat of miscarriage, influenza in the first trimester, Type 1 or 2 DM and some drugs such as isotretinoin. Especially noteworthy in our study was the threat of miscarriage (presented in 19.6% of our patients), the history of which has been mentioned earlier; the other significant antecedent found was the presence of Type 2 DM in 4.1% of the patients, which has been shown to be related.

The type of microtia found most often was Grade iii microtia/atresia (in 33% of the cases). This is probably due to the fact that the more extreme the malformation, the more likely the consultation. Another reason is that our patients presented more severe hypopacisis, which is a feature not well explained in the world literature, and is the reason for consultation in our institution.

Two thirds of our patients presented unilateral microtia. This agrees with the literature, being described as the most common malformation, with the right side being the one most often involved.

With respect to the presence of a family history of microtia, we found that the prevalence was high, nearly 25%. In contrast, many populations described in the literature show a lower prevalence, generally below 10% and seldom higher than 15%. This situation, together with a low prevalence of consanguinity and inbreeding, lends support to the possibility of autosomal-dominant inheritance, with variable expressivity. However, other hereditary possibilities cannot be ruled out.

Experiments with gene inactivation have identified some that are necessary for the formation of middle ear components. Examples are ET-1 and FGF-8, which probably mediate epithelial-mesenchymal interactions; other genes (Eya1, Prx1, Hoxa1, Hoxa2, Dlx1, Dlx2, Dlx5 and Gsc) have been shown to be involved in the processes of modelling and morphogenesis of the mesenchymal cell derivatives. Genetic expression of Tbx1 plays a key role in the formation of the middle and outer ear in mice. Mutant mice homozygous for Tbx1 have defects in the development of the middle and outer ear. This gene is also important for the formation of the otic vesicle, as has been observed in knock-out mice, in which there is a failure in the formation of the sensory organs of the inner ear. This gene is very probably necessary for the development of sensory organs and for the
suppression of neural cell fate in the otic vesicle (Table 2). The fact that the rest of the systems involved in FAV spectrum also depend on mesenchymal tissue makes us think that these same genes are probably involved in the presentation of malformations other than microtia. However, the possibility that other genes are related cannot be ruled out either.

In conclusion, we can say that, in the majority of familial cases, it is very probable that there is involvement of a gene that has a dominant effect but that has variable expressivity and reduced penetration. However, in many other cases, it is feasible that other genes are included in the presentation of this spectrum, in which many areas and many different tissues are affected. That is to say, that much remains to investigate about this disease.

Conflict of Interests

The authors have no conflict of interests to declare.

References