Deafness secondary to genetic syndromes: A review

Marques JS

Pediatric Department - Genetic outpatient - Centro Hospitalar Vila Nova de Gaia/Espinho – Portugal

Abstract
Background
Deafness may be classified in: conductive, sensor neural, mixed, and central type. The degree of severity is divided in: low, moderate, severe and profound. Among other causes, genetic syndromes are responsible for hearing loss in an important number of cases.

Methods
We review cases from our genetic consultation which causes conductive, sensorineural, mixed and central hearing loss.

Results
We find four cases of conductive hearing loss- Treacher-Collins, Pierre-Robin, Gondenhar and Crouzon syndromes; one case of recessive sensor neural deafness- Jervell-Lange-Nielsen; seven cases of dominant sensor neural deafness- Waardenburg type 1, neurofibromatosis type 1, Noonan, Turner, Patau, CHARGE association and Zellweger; one case of recessive x-linked sensor neural deafness; Hunter, one case of mitochondrial hearing loss, two cases of mixed deafness; Stickler and Larsen.

Conclusion
The sooner we identify genetic syndromes responsible for sensor neural deafness and conductive hearing loss, the easier will be for us to do the genetic counseling in the future pregnancy.

Introduction
Deafness occurs in 1 to 2 per 1000 newborns and in 2 per 1000 young children. The prevalence of moderate deafness, severe and profound is around 1/900 to 2500 newborns.

Hearing loss may be classified in: conductive (involving any cause that in some way limits the amount of external sound that gains access to the inner ear), sensor neural (involving the inner ear, cochlea, or the auditory nerve, which is a combination of conductive and sensor neural hearing loss) and central, involving higher brain centers and auditory neuropathy or auditory neuropathy spectrum disorder.

The degree of severity is divided in: low (20 a 40 dB), moderate (41 a 60 dB), severe (61 a 90 dB) and profound (>90 dB).

The external ear develops between 8-28 weeks of gestational age.

Absent, malformation or stenosis of the external ear, are responsible for conductive hearing loss, in most cases with moderate degree of severity [1,2,3,4].

The genetic syndromes which causes this conductive hearing loss are: Treacher-Collins, Pierre-Robin, Gondenhar and Crouzon syndromes [5,6,7,8].

Sensor neural deafness occurs in 1/2000 newborns. Genetic cause is responsible for 50% of total cases:

- 80% recessive
- 15% dominant
- 2% X – linked (more recessive)
- 1% mitochondrial

The recessive sensor neural deafness is caused by: Pendred, Jervell-Lange-Nielsen and Alport syndromes [9,10,11].

“The most frequent genetic dominant hearing loss is: Waardenburg type 1 and 2, Neurofibromatosis type 1, Patau, Noonan, Turner, CHARGE and Zellweger [12,13,14,15,16,17,18].

Hunter and Alport are the genetic syndromes responsible for x-linked deafness [19, 20].

Mitochondrial disease is a rare cause, with only 1% of all cases presenting as sensor neural hearing loss [21].

The mixed causes of hearing loss are attributed to CHARGE, Sticker and Larsen syndromes [22,23].

Methods
We review cases from our genetic consultation of Pediatric Department of Centro Hospitalar Vila Nova de Gaia/Espinho, which causes conductive, sensorineural, mixed and central hearing loss.

Results
We find four cases of conductive hearing loss- Treacher-Collins,
Pierre-Robin, Gondenhar and Crouzon (Figures 1);

one case of recessive sensor neural deafness-Jervell-Lange-Nielsen;

"six cases of dominant sensor neural deafness- Waardenburg type 1", neurofibromatosis type 1, Noonan, Turner, Patau and Zellweger;

one case of recessive x-linked sensorineural deafness- Hunter;

one case of mitochondrial hearing loss

and three cases of mixed deafness- CHARGE association, Stickler and Larsen.

Gene studies were performed in all cases requiring molecular confirmation: Jervell-Lange-Nielsen, Waardenburg type 1, neurofibromatosis type 1, Noonan, Hunter and mitochondrial disease.
All syndromes are resumed in Tables 1-6.

### Table 1: Conductive hearing loss

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INHERITANCE</th>
<th>HEARING LOSS</th>
<th>MAJOR FEATURES</th>
<th>MOLECULAR STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treacher-collins</td>
<td>Autosomal dominant</td>
<td>Conductive</td>
<td>Malar hypoplasia, Malformation of auricle, Downward slanting palpebral fissures, Lower eyelid coloboma, Cleft palate, Mandibular hypoplasia</td>
<td>TCOF1</td>
</tr>
<tr>
<td>Pierre-Robin</td>
<td>Autosomal recessive, X-linked form and associated with trisomy 18 and other syndromes</td>
<td>Conductive</td>
<td>Robin sequence, Micrognathia, Retroglossia, U-shaped posterior cleft palate</td>
<td>SOX9</td>
</tr>
<tr>
<td>Gondonhar</td>
<td>Autosomal dominant</td>
<td>Conductive</td>
<td>Facial asymmetry, Unilateral external ear deformity, Preauricular tags, External auditory canal atresia, Microtia, Upper eyelid coloboma, Cleft palate, Ventricular septal defect, Multicystic dysplastic kidney, Vertebral anomalies, Arnold-Chiari malformation, Agenesis of corpus callosum</td>
<td>TCOF1, EYA1, SALL1</td>
</tr>
<tr>
<td>Crouzon</td>
<td>Autosomal dominant</td>
<td>Conductive</td>
<td>Craniosynostosis, Brachycephaly, Frontal bossing, Maxillary hypoplasia, Mandibular prognathism, Proptosis, Shallow orbits, Cervical spine abnormalities</td>
<td>FGFR2</td>
</tr>
</tbody>
</table>

### Table 2: Sensorineural deafness - dominant

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INHERITANCE</th>
<th>HEARING LOSS</th>
<th>MAJOR FEATURES</th>
<th>MOLECULAR STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waardenburg</td>
<td>Autosomal dominant</td>
<td>sensorineural deafness</td>
<td>Dystopia canthorum, Heterochromia iridis, Hypopigmented skin lesions, Premature graying of hair</td>
<td>PAX3</td>
</tr>
<tr>
<td>type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Waardenburg</td>
<td>Autosomal dominant</td>
<td>sensorineural deafness</td>
<td>Hypopigmented irides, Anosmia, Premature graying, Axial hypotonia, Increased muscle tone</td>
<td>SOX10</td>
</tr>
<tr>
<td>type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Autosomal dominant</td>
<td>sensorineural deafness</td>
<td>Lisch nodules, Neurofibromas, Plexiform neurofibroma, Cafe-au-lait spots, Axillary freckling, Optic glioma</td>
<td>NF1</td>
</tr>
<tr>
<td>type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patau</td>
<td>Unknown</td>
<td>sensorineural deafness</td>
<td>Holoprosencephaly, colobomata of iris, clef lip, clef palate, polidactaly, ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td>Noonan</td>
<td>Autosomal dominant</td>
<td>sensorineural deafness</td>
<td>Short stature, Micognathia, Webbed neck, Pulmonic stenosis, Cubitus valgus, Low posterior hairline, Articulation difficulties</td>
<td>PTPN11</td>
</tr>
<tr>
<td>Turner</td>
<td>Unknown</td>
<td>sensorineural deafness</td>
<td>Short stature, congenital lymphedema of the hands and feet, webbed neck, high-arched palate, and short fourth metacarpal.</td>
<td></td>
</tr>
<tr>
<td>Zellweger</td>
<td>Autosomal recessive</td>
<td>sensorineural deafness</td>
<td>Large fontanelles, High forehead, Pigmentary retinopathy, Pulmonary hypoplasia, Ventricular septal defects, pyloric hypertrophy, Hepatomegaly, Hypotonia, areflexia</td>
<td>PEX1, PEX2, PEX3, PEX5, PEX6, PEX12, PEX14, PEX26</td>
</tr>
</tbody>
</table>
Conclusions

In our review, we did not find any case of central deafness. Two of the most frequent causes of recessive conductive hearing loss (Pendred and Alport) and dominant sensor neural deafness (Warrensburg type 2) were also not detected.

The sooner we identify genetic syndromes responsible for sensor neural deafness and conductive hearing loss, the easier will be for us to do the genetic counseling in the future pregnancy.

Summary

Deafness occurs in 1 to 2 per 1000 newborns and in 2 per 1000 young children. Hearing loss is classified in: conductive, sensor neural, mixed and central type. The degree of severity is divided in: low (20 to 40 dB), moderate (41 to 60 dB), severe (61 to 90 dB) and profound (>90 dB).

Deafness has many causes, but genetic syndromes play an important role in his etiology.

In this review, we will talk about deafness secondary to the most important genetic syndromes.
References