Original Article

Evaluation of Family History of Permanent Hearing Loss in Childhood as a Risk Indicator in Universal Screening

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Introduction and objective: Sixty percent of prelingual hearing loss is of genetic origin. A family history of permanent childhood hearing loss is a risk factor. The objective of the study is to determine the relationship between this risk factor and hearing loss. We have evaluated clinical and epidemiological characteristics and related nonsyndromic genetic variation.

Material and method: This was a retrospective, descriptive and observational study of newborns between January 2007 and December 2010 with family history as a risk factor for hearing loss using transient evoked otoacoustic emissions and auditory brainstem response.

Results: A total of 26,717 children were born. Eight hundred and fifty-seven (3.2%) had family history. Fifty-seven (0.21%) failed to pass the second test. A percentage of 29.1 (n=16) had another risk factor, and 17.8% (n=9) had no classical risk factor. No risk factor was related to the hearing loss except heart disease. Seventy-six point four percent had normal hearing and 23.6% hearing loss. The mean of family members with hearing loss was 1.25. On genetic testing, 82.86% of homozygotes was normal, 11.43% heterozygosity in Connexin 26 gene (35delG), 2.86% R143W heterozygosity in the same gene and 2.86% mutant homozygotes. We found no relationship between hearing loss and mutated allele.

Conclusions: The percentage of children with a family history and hearing loss is higher than expected in the general population. The genetic profile requires updating to clarify the relationship between hearing loss and heart disease, family history and the low prevalence in the mutations analyzed.

KEYWORDS
Risk factor; Early detection; Hereditary hearing loss

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PALABRAS CLAVE
Factor de riesgo; Detección precoz; Hipoacusia hereditaria

Evaluación de la historia familiar de hipoacusia permanente en la infancia como factor de riesgo en el cribado universal

Resumen
Introducción y objetivo: El 60% de las hipoacusias prelinguales tienen un origen genético. Entre los factores de riesgo se encuentra el antecedente familiar de hipoacusia permanente en la infancia. El objetivo del estudio es conocer la relación entre este factor de riesgo y la hipoacusia, evaluándose características clínico-epidemiológicas y si existe variación genética no síndromica relacionada.
Material y método: Estudio retrospectivo, transversal, descriptivo y observacional de los recién nacidos entre enero de 2007 y diciembre de 2010 con factor de riesgo de antecedente familiar de hipoacusia mediante otoemisiones acústicas provocadas transitorias y potenciales evocados auditivos de tronco cerebral.
Resultados: Nacieron 26.717 niños. Ochocientos cincuenta y siete (3,2%) tenían antecedente familiar. Cincuenta y siete (0,21%) no pasan segundas otoemisiones. Un 29,1% (n = 16) tenían otro antecedente de riesgo añadido. Un 17,8% (n = 9) tenían factor de riesgo no clásico. Ningún factor de riesgo tenía relación con la hipoacusia, excepto la cardiopatía. Según potenciales, el 76,4% tenían normoaudiación y el 23,6%, hipoacusia. La media de familiares hipoacúsicos es de 1,25. En test genéticos el 82,86% son homocigosis normal, el 11,43% heterocigosis para mutación 35delG del gen de la Conexina 26, el 2,86% heterocigosis R143W del mismo gen y el 2,86% homocigosis mutante 35delG. No se encuentra relación entre hipoacusia y tener un alelo mutado.
Conclusiones: El porcentaje de niños con antecedente familiar diagnosticado de hipoacusia es superior a lo esperado en la población general. Es necesaria la actualización del perfil genético para esclarecer la relación encontrada entre hipoacusia con cardiopatía, el número de familiares afectos y la baja prevalencia en las mutaciones analizadas.
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Introduction
Hearing is the natural way of acquiring language. Consequently, deafness is a serious impediment whose effects go far beyond the impossibility of speaking. Child hearing loss is a condition clearly differentiated from that of adult hearing loss because of everything it implies in social and intellectual development, and whose disabling and incapacitating potential can be resolved in terms of how early diagnosis is reached and appropriate treatment and rehabilitation are started.\(^1,2\)

Hearing loss can arise from genetic (50%), environmental (25%) or unknown (25%) origins. Ones caused by heredity represent 20%-25% of the syndromic cases, while they are some 75% of the nonsyndromic cases. Within the latter, 50% are due to a single gene, the Connexin 26 gene.\(^3\)

Inherited hearing loss can be transmitted as autosomal dominant (10%-20%), autosomal recessive (70%-80%), X-linked inheritance (1%-5%) or inheritance through mutations in mitochondrial DNA (3%). More than 100 genes responsible for nonsyndromic hearing loss that codify products with highly varied functions have been identified.

Approximately 60% of hearing loss before the acquisition of language is of genetic origin and a great percentage of hearing loss in general probably has undemonstrated genetic influence in normal healthcare practice. The contribution of the \(GJB2\) gene (Connexin 26) has modified the assessment of children with hearing loss.\(^1\) As a group, the mutations in the \(GJB2\), \(GJB3\) and \(GJB6\) genes constitute the most frequent cause of nonsyndromic hereditary hearing loss in our milieu. The \(GJB2\) gene mutations are the most frequent cause of autosomal recessive nonsyndromic hearing loss.\(^1\) More than 100 pathogenic variations of this gene have been identified, the most common of the recessive hearing loss cases (more than 80%) being the 35delG mutation.\(^1,3,5\) About 1%-3% of the general population are carriers.\(^4\)

The Joint Committee on Infant Hearing (JCIH) establishes criteria for risk of hearing loss validated by the Spanish Commission for Early Detection of Hearing Loss (Spanish acronym: CODEPEH). Before universal screening was instituted, auditory tests focused on children having these risk factors (RFs), given that the incidence of hearing loss was 40–50 times greater in this collective.\(^6\) Family history of permanent hearing loss in infants (FPHLI) falls among these RFs.

The objective of this study was to determine the relationship between the RF for FPHLI and sensorineural hearing loss in the children born in the 2007-2010 period. The clinical-epidemiological characteristics of the children who went through a universal hearing loss screening program and those who failed it were analyzed, establishing the presence and degree of hearing loss, as well as whether any nonsyndromic genetic variation existed.
Evaluation of Family History of Permanent Hearing Loss as a Risk Indicator

Material and Method

This was a transversal, retrospective, descriptive observational study of the newborns (NBs) between 1 January 2007 and 31 December 2010 presenting FHPHLI as a RF for hearing loss that were included in the Universal Hearing Loss Screening Program. The data were taken from the Program for Early Detection of Deafness database in our autonomous community. The corresponding case histories were reviewed. We limited ourselves to this 4-year period before including the automatic potentials in the diagnostic algorithm, so that the descriptive results would not be modified with a 5-year follow-up of the children after the hearing loss diagnosis.

The initial examination was carried out in the maternity ward by detecting otoacoustic emissions using portable automated hearing screening devices (Echo-Screen TA Plus). All the NBs were sent to the second phase, in which transient evoked otoacoustic emissions were detected using Intelligent Hearing Systems (TE audio test). If the transient evoked otoacoustic emissions were absent in both ears, the NBs were referred to the Hearing Loss Unit for diagnosis using brainstem auditory evoked potentials (BAEP) (Fig. 1).

The dependent variable was hearing loss and the independent ones were basic epidemiological factors related to the birth, neonatal RF, RF for hearing loss and when the various screening tests were performed.

Genes were studied using polymerase chain reaction (PCR) techniques and high-resolution electrophoresis, analysing the 35delG mutation of Connexin 26, the R143W mutation in the same gene and the 12sRNA gene in the mitochondrial DNA seeking the A1555G mutation (related to aminoglycosides). Homo- or heterozygosis mutation was checked using specific allele analysis.

Statistical analysis was performed with SPSS 20.0 (IBM) for Windows. Quantitative variables are shown with mean and standard deviation (SD), as well as confidence interval (CI) at 95%. Qualitative variables are shown in percentage. To test the association of these variables, Pearson Chi square was used; for means, Student’s t-test was used, and non-parametric tests such as the Mann–Whitney U were used to compare medians. An error of $\alpha=0.05$ was set for the statistical tests.

Results

In the 2007–2010 period, there were 26,717 live NBs in the records for neonatal screening for hearing loss. Some RF was shown for 4674 children (17.5%) and, of these, 857 had FHPHLI as the RF (3.2%).

Of the 857 children with RF for FHPHLI, 800 children passed the second test for transient evoked otoacoustic emissions and 57 (6.65%) failed; that is, 0.21% of the total NBs. Of these 57, 2 were lost during the study because no clinical data was kept due to transfer.

Of these 55 NBs, 22 were male (40%) and 33, female (60%). No statistically significant relationship was found between sex and (odds ratio [OR] 0.37; 95% CI 0.07–1.98) (P=.23). Mean weight at birth was 3153.73 ± 708.3 g. None of the children with low weight (less than 2500 g) presented hearing loss. Weights were similar between groups of infants with and without hearing loss (P=.75).

Oxygen therapy was required by 9.09% (n=5) of the NBs at birth. None of them presented hearing loss. Mean Apgar score at 1 minute was 8.5 ± 1.28 and at 5, 8.92 ± 0.28. Pathological Apgar score (lower than 7) was obtained by 1.82% (n=1); this single child had hearing loss. All the children had Apgar scores at 5 min within normal ranges. Mean gestational week at birth was 38.88 ± 2.09 weeks. The distribution of gestational age was 90.91% (n=37) at term (37 weeks or more), 7.27% (n=3) preterm (34–37 weeks), 1.82% (n=2) premature (28–34 weeks) and there were no children with extreme prematurity (fewer than 28 weeks). No child with fewer than 37 weeks had hearing loss. We found no statistically significant difference in gestational age between the groups with and without hearing loss (P=.17).

As for the RF for hearing loss described by the JCIH, 9.09% (n=5) had to be admitted to the neonatal intensive care unit for more than 5 days. None presented hearing loss. Phototherapy for hyperbilirubinemia was required by 5.45% (n=3). Of these, 33.3% had hearing loss. We found no statistically significant relationship between phototherapy-treated hyperbilirubinemia and hearing loss (OR 2.75; 95% CI 0.22–34.04). None of the 9.09% children (n=5) that underwent assisted ventilation had hearing loss. Some type of craniofacial anomaly was present in 3.63% (n=2). Neither had hearing loss. Some type of endocrinological illness was presented by 1.82% (n=1). This child, diagnosed with diabetes mellitus, had no associated hearing loss. Some type of ototoxic drug was given to 14.54% (n=8); in all the cases, it was antibiotics. There was no statistically significant relationship between the ototoxic drug and hearing loss (OR 1.9; 95% CI 0.32–11.41). Some type of intrauterine infection caused by the TORCHES group was shown in 1.82% infants (n=1). This single child, diagnosed with cytomegalovirus, had hearing loss. Syndromes linked to hearing loss or progressive hearing loss were presented in 1.82% (n=1). This infant, with neurofibromatosis, showed no hearing loss.

Another RF in addition to FHPHLI was present in 29.1% of the NBs (n=16). Of the NBs that showed hearing loss
(n=9), 33.33% (n=3) had 1 or more RFs. We found no statistically significant relationship between hearing loss and having another RF (OR 1.27; 95% CI 0.28–5.85). The NBs with hearing loss had a mean of 1.56 (±1.01) RFs, while those with normal hearing had a mean of 1.37 (±0.68). We found no difference in mean RF between the groups with and without hearing loss (P=.943).

We consider other RFs for non-classic hearing loss (not defined by the JCIH) as being circumstances that may cause hearing loss either by themselves or through their syndromic association. Some type of neuropathy was present in 5.45% (n=3), but none of these infants had hearing loss. Some type of cardiopathy was presented by 9.09% (n=5), of which 60% (n=3) had hearing loss. There was a statistically significant relationship between cardiopathy and hearing loss (OR 11; 95% CI 1.52–79.84; P=.006). In 1.82% (n=1), there was mild motor delay; this child showed no hearing loss. There were no cases of retinopathy of prematurity or of admission to Neonatology for infection or sepsis.

Non-classic RFs were presented by 17.8% (n=9). Of those that presented hearing loss, 44.44% (n=4) had non-classic RFs. We found a statistically significant relationship between hearing loss and having non-classic RFs (OR=6.56; 95% CI 1.31–32.8). The NBs presenting hearing loss had a mean of 0.44 (±0.53) non-classic RFs, whereas the mean was 0.11 (±0.31) in the normal-hearing infants. There was no statistically significant difference in the mean number of non-classic RFs between the groups with and without hearing loss (P=.22).

Of the 55 NBs studied, 41.8% (n=23) did not undergo the test of potentials, given that it was shown that they had normal hearing when the Tanaka Test was administered to them. Of the 58.2% (n=32) that did undergo a BAEP test, 53.1% (n=17) passed the first test, with normal hearing results. Of the 46.9% (n=15) that failed the first BAEP, a second test was administered to 33.3% (n=8), 25% (n=2) of them passing it and being considered as having normal hearing. We concluded that 76.4% (n=42) of the NBs can hear and 23.6% present hearing loss (n=13) according to BAEP results. Of the 23.6% (n=13) of NBs with hearing loss, 92.3% (n=12) have bilateral loss. The distribution was: 7.7% (n=1) unilateral sensorineural hearing loss in the right ear, 53.8% (n=7) bilateral sensorineural, 7.7% (n=1) unilateral-bilateral mixed and 30.8% (n=4) bilateral transmission hearing loss (Fig. 2).

In the right ear, 76.4% (n=42) had normal hearing based on the BAEP results. The distribution of hearing loss type was 14.5% (n=8) sensorineural, 7.3% (n=4) transmission and 1.8% (n=1) mixed. The mean in decibels (dB) was 52.69 ± 30.18; 7.3% (n=4) had mild hearing loss; 10.9% (n=6), moderate; and 5.5% (n=3), profound. In the left ear, 78.2% (n=43) had normal hearing. The loss level distribution was 12.7% (n=7) left sensorineural, 7.3% (n=4) transmission and 1.8% (n=1) mixed. The mean was 51.67 dB, with 3.6% (n=2) mild, 12.7% (n=7) moderate, 1.8% (n=1) severe and 3.6% (n=2) profound.

Ear computed axial tomography (CAT) scan was performed on 5.5% (n=3) of the NBs. In 3.6% (n=2), the result was normal; the CAT scan was done in the context of a previous study for cochlear implant. In the remaining 1.2% (n=1), the result was chronic otitis media, in a patient with bilateral mixed hearing loss who was fitted with hearing aids. No study patients required a magnetic resonance when they were screened; later on, in agreement with the cochlear implant protocol, they did.

In 3.6% (n=2) of the NBs, a cochlear implant was necessary, while 3.6% (n=2) required hearing aids. In 2 patients, the waiting period before cochlear implant placement was 364 and 330 days from birth, and 321 and 202 days from hearing loss diagnosis, respectively. The waiting period for audio prosthesis fitting for the 2 patients with hearing aids was 2238 and 649 days and, from diagnosis, 403 and 216 days, respectively.

All the children had a history of, at least, 1 relative with FHPHLI. The mean was 1.25 (±0.58) family members. In the group with hearing loss (n=9), the mean was 1.89 (±0.93) relatives and 1.13 (±0.4) in the group with normal hearing (n=46). We found a statistically significant relationship between hearing loss and having more than 1 relative with h(n=earing loss (P=.001). The degree of kinship of the affected family member for the individuals for whom this information is available was: 32.26% (n=10), 1 of the parents; 6.45% (n=2), siblings; 25.81% (n=8), grandparents; 9.68% (n=3), aunts and uncles; and 25.81% (n=8), other relative (Fig. 3).

For the cases in which the information was known, the treatment for the relative with hearing loss was: 33.3% hearing aids, 20% cochlear implant, 26.7% sign language communication and 20% no treatment.
A gene study was done for 63.6% (n=35) of the children. All the karyotypes yielded a normal chromosome result. In 82.86% (n=29), the result was normal homozygote for all the mutations studied; in 11.43% (n=4), heterozygosis for the 35delG variant; in 2.86% (n=1), heterozygosis for R143W; and in 2.86% (n=1), mutant homozygosis for 35delG was found. For this child, the definitive diagnosis was sensorineural hearing loss of genetic origin. We found no statistically significant relationship between hearing loss and having at least 1 mutated allele in the variations studied (OR 1.92; 95% CI 0.28–13.08).

In the case of the 2 infants with a cochlear implant, the genetic result was normal in 1 patient, while gene study was not done on the other. As for the 2 children with hearing aids, both had a result of normal homozygosis normal for the mutations analyzed. In the single case of homozygous 35delG mutation, the treatment for communication was sign language, given that both parents were hearing impaired and rejected the cochlear implant option.

Discussion

Of the total NBs studied in the Early Hearing Loss Detection program between January 2007 and December 2010, 3.2% had FHPHLI as the RF, with it being the second-most frequent RF, behind ototoxic drug administration (16.14%). This is the same order of frequency that Trinidad-Ramos found (1.5% of that population); the percentage of NBs with problems in otoacoustic emissions was higher in those having family histories. That researcher concluded that the FHPHLI RF affected the test result. Out of a total 742 ears, 17 with pathological potentials were identified, representing 2.29%; no statistically significant differences between the children with and without a family history were found. In our series, we found pathological results in 25 ears (out of 110 studied), constituting 22.72%; having a family history 1.52% of the children (n=857) and 0.05% of the total NBs (n=26,717).

Several authors have found that profound sensorineural hearing loss in children with RFs represents from 1% to 3%.7-10 The results we obtained show that 5.5% of the NBs had sensorineural hearing loss. For both profound hearing loss and for all the levels of auditory impairment, the percentage of hearing loss in our study is higher than that of other studies for all the RFs, making the weight of this family history evident in the incidence of hearing loss. Santos finds a hearing loss of 31.64% in children with the RF for HFHN; however, these were not children from universal neonatal screening, but rather a percentage of children referred for consultation because of established suspicion of hearing loss.

When the JCIH define the RF for hearing loss, they estimate that 1 or more are going to present in around 6%–8% of the NBs. In this group, the incidence of deafness is greater than in other infants. Between 50% and 75% of the children with bilateral moderate to profound hearing loss have 1 or more RFs, representing some 4%–7% of the total population.12,13

Erenberg et al.14 and Ptok15 find that the rate of sensorineural hearing loss among the NBs presenting some associated RF is 1%–2%. A 2009 study by Ohl et al.16 on a total of 1461 NBs with RFs linked to sensorineural hearing loss indicates that having 2 or more RFs significantly increases bilateral hearing loss. Bielecki et al.17 also note a greater incidence of hearing loss in NBs presenting a auditory RF in analysing 5282 children; they show a frequency of 3.15%–3.51% of hearing loss with 1 or 2 RFs, 5.4%–5.6% when there are 3 or 4 associated RFs and, in the children with 5 or more RFs, the probability almost doubles: 9.46%–10.53%. Their conclusion is that for auditory alteration, the most common RFs in order of importance are the use of ototoxic drugs, prematurity, very low birth weight and intensive care stays of more than 7 days. Tiensoli et al.18 find that the main RFs are the use of ototoxic drugs in first place, followed by stay in incubators, the need for mechanical ventilation and birth weight less than 1500 g.

In a study on birth weight less than 1500 g, Borkoski-Barreiro et al.19 note that hearing loss is always associated with 1 or 2 auditory RFs more, with the use of ototoxic drugs and the presence of hyperbilirubinemia being the most frequent. They indicate that the extent to which very low birth weight alone increases the prevalence of hearing loss in the neonatal period is still unclear; the results from several studies show that the combination of RFs and general condition, more than only low birth weight, is crucial in developing hearing loss. Oviedo-Santos find that ototoxicity is associated with another RF in 90% of the NBs. In our study, 29.1% of the NBs had another RF associated. We note that low birth weight, prematurity, stay in intensive care and the use of an ototoxic drug coexist in children frequently. However, this is not true of FHPHLI, which is probably the most independent RF.

Of the non-classic RFs, we have found that there is a statistically significant association between cardiology and hearing loss. Mutations related to hearing loss are not usually identified in our setting as a normal practice, except for those more frequent in the GJB2 gene.20-23 Bearing in mind the results of our study on inheritance, we could postulate that a hypothetical explanation of this deafness-linked cardiopathy could be that related genetic variations that we have not identified might exist.

In many studies, FHPHLI appears at the top of the list of the RFs. However, for various authors (such as Kountakis et al.24), this is not a very useful variable, given that it is improperly documented in the majority of NBs. This family history has not even got a statistically significant relationship with deafness in some studies. Nevertheless, in others (such as that of Olh et al.16), this RF is indeed found to be associated with hearing loss.

In our results, the study of the affected relatives is of note. We find that, in up to 43.6%, the individual that is affected with hearing loss is unknown and, consequently, the treatment is as well. This coincides with the indication of Kountakis et al.24 but it must be remembered that the years covered in this study are the first 3 after institution of screening in our area, where progressive modifications to improve the lack of data have been implemented.

We obtain a statistically significant relationship between hearing loss and the number of relatives affected, with deafness being more probable in the infant if there is more than 1 relative with hearing loss. We could therefore use this fact, when initiating genetic studies, to consider having more than 1 relative affected by sensorineural hearing loss in infancy as a criterion.
In 2009, the International Journal of Audiology published a meta-analysis about the presence of the 35delG mutation (GJB2 gene) and its relationship to non-syndromic sensorineural hearing loss in various continents. The highest average of carriers was detected in southern Europe. Detection of the 35delG mutation varied in the populations from 28% to 63%. In addition, the mutation of the GJB6 gene has been identified as the second most frequent mutation from a nonsyndromic cause.25

In the Spanish population, 60%–70% of nonsyndromic familial hearing loss cases are due to alterations in the GJB2 gene. In their patients, Ramos et al.26 have found that the 35delG mutation is the most frequent (50%), followed by that of R143W (7.5%), both in the GJB2 gene. We obtain low prevalence of positive gene study, which differs from the previous analyses in Spanish population studied by Ramos et al. and does not coincide with what would be expected for children whose RF is FHPHLI. It seems logical to consider the possibility, not unlikely, that they present a hereditary variation related to hearing loss that we have not identified.

Speaking generally, whether all NBs with the RF for FHPHLI should undergo gene studies is not well standardised. Depending on the population being studied, our knowledge about its genetic characteristics and our economic and diagnostic possibilities, we will decide which genetic mutations must be established. To evaluate this properly, it has to be based on studies correctly identifying the relatives that have hearing loss and on adequate data collection; however, we should not limit ourselves to only the parents, given that it has been seen that in up to 95% of the children with hearing loss revealed by universal screening, both parents had normal hearing.27

One limitation of this study is its descriptive nature. Another is that the number of patients is limited and, consequently, it is susceptible to bias when establishing causalities. Nevertheless, its usefulness lies in the possibility of obtaining various conclusions and lines of work.

Conclusions

We can emphasise 3 relevant facts. First, the low prevalence that we find in pathological gene studies on the GJB2 gene in a group at risk for FHPHLI is at odds with other studies. A new updated review would be necessary, one in which the genetic profile of the population with hearing loss in our community in general is re-evaluated, as well as that of the subpopulation with this RF specifically. Second, the statistically significant relationship of cardiopathy in children with hearing loss has to be remembered in this new update, to attempt to clarify the relationship there is. And finally, in our hospital’s Clinical Genetics protocol, indications could be created with respect to deciding to begin gene studies on a patient, bearing in mind the number of relatives with sensorineural hearing loss in infancy as a criterion, given that we have identified a statistically significant relationship with hearing loss if there is more than 1 relative affected.

Conflict of Interests

The authors have no conflicts of interest to declare.

References


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