The Relationship Between Neonatal Hyperbilirubinemia and Sensorineural Hearing Loss

Cándido Corujo-Santana, Juan Carlos Falcón-González, Silvia Andrea Borkoski-Barreiro, * Daniel Pérez-Plasencia, Ángel Ramos-Macías

Unidad de Hipoacusia, Servicio de Otorrinolaringología y Patología Cérvico Facial, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain

Received 20 September 2014; accepted 20 October 2014

Abstract

Introduction and Objective: Severe jaundice that requires exchange transfusion has become a relatively rare situation today. About 60% of full term neonates and 80% of premature ones will suffer from jaundice within the first week of life.

Hyperbilirubinemia at birth is a risk factor associated with hearing loss that is usually further linked to other factors that might have an effect on hearing synergistically. This study aimed to identify the relationship between hyperbilirubinemia at birth as a risk factor for sensorineural hearing loss in children born at Complejo Hospitalario Universitario Insular-Materno-Infantil de Gran Canaria, in the 2007–2011 period.

Method: This was a retrospective study of 796 newborns that had hyperbilirubinemia at birth, using transient evoked otoacoustic emissions and evoked auditory brainstem response.

Results: Hundred eighty-five newborns (23.24%) were referred for evoked auditory brainstem response. Hearing loss was diagnosed for 35 (4.39%): 18 neonates (51.43%) with conductive hearing loss and 17 (48.57%) with sensorineural hearing loss, 3 of which were diagnosed as bilateral profound hearing loss. Half of the children had other risk factors associated, the most frequent being exposure to ototoxic medications.

Conclusions: The percentage of children diagnosed with sensorineural hearing loss that suffered hyperbilirubinemia at birth is higher than for the general population. Of those diagnosed, none had levels of indirect bilirubin ≥20mg/dl, only 47% had hyperbilirubinemia at birth as a risk factor and 53% had another auditory risk factor associated.

© 2014 Elsevier España, S.L.U. and Sociedad Española de Otorrinolaringología y Patología Cérvico-Facial. All rights reserved.
Introduction

Permanent hearing loss in infancy is an important public health problem. It affects 1/1000 live newborn babies (NBB) if we only take into account neurosensorial hearing loss (NHL) that is congenital, deep and bilateral, and 5/1000 live NBB if all degree of hearing loss are taken into account.1

Hearing loss not only permanently affects the development of oral language, as it may also affect development in general as well as emotional and social development.2

Criteria or risk factors associated with hearing loss were established in 1994 and revised in the year 2000. 10%–30% of NBB would fulfill one of these criteria, and hyperbilirubinemia at birth is one of them. Severe jaundice requiring exchange transfusion is now relatively rare. Approximately 60% of newly born babies at term and 80% of preterm babies will have jaundice during the first week of life.

NBB with hyperbilirubinemia amount to 2.30% of the total population of NBB. Hyperbilirubinemia at birth is a risk factor associated with hearing loss that is generally associated with others that may have a synergic effect on hearing, and therefore the risk of hearing loss is substantially higher than it is in children that do not present these.3

The early detection and treatment of these problems will largely determine the quality of life of these children in the future. It is therefore necessary to periodically monitor certain aspects of children, including the evaluation of hearing.3

The aim of this article is to establish the relationship that exists between hyperbilirubinemia at birth as a risk factor of NHL in children born in the Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, during the period 2007–2011 and included in the Program for the Early Detection of Childhood Hearing Loss.

Materials and Methods

A retrospective study was carried out of 796 NBB who presented the diagnosis of perinatal hyperbilirubinemia as a risk factor and who were included in the Program for the Early Detection of Childhood Hearing Loss of the Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria.

In the autonomous community of the Canary Islands the Program consists of a system of universal screening of the population in two phases (Fig. 1).

The first examination takes place in the maternity ward during the first 48 h of life, taking advantage of the mother’s hospitalisation. The technique used is the detection of otoacoustic emissions using portable automatic devices (Echo-ScreenTA Plus®). All NBB were sent to the second phase in which otoacoustic emissions were detected using Intelligent Hearing Systems and Interacoustic systems.

If the resulting transitory otoacoustic emissions are absent from both ears patients were referred to the Hearing Loss Unit of the Ear, Nose and Throat department for

---

**PALABRAS CLAVE**

Hyperbilirubinemia; Hipoacusia neonatal; Screening auditivo neonatal

---

**Relación entre hiperbilirrubinemia neonatal e hipoacusia neurosensorial**

**Resumen**

**Introducción** y objetivos: La ictericia severa que precisa exanguiotransfusión se ha convertido en una situación relativamente rara en la actualidad. El 60% de los neonatos a término y el 80% de los pretermino se pondrán ictericos dentro de la primera semana de vida.

La hiperbilirrubinemia al nacer es un factor de riesgo asociado a hipoacusia que generalmente se asocia a otros que podrían tener efecto sobre la audición de manera sinérgica. El objetivo del estudio es establecer la relación entre la hiperbilirrubinemia al nacer como factor de riesgo de hipoacusia neurosensorial en los niños nacidos en el Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, periodo 2007–2011.

**Método:** Estudio retrospectivo de 796 recién nacidos con hiperbilirrubinemia al nacer, mediante otoemisiones acústicas provocadas transitorias y potenciales evocados auditivos de tronco cerebral.

**Resultados:** Ciento ochenta y cinco recién nacidos (23,24%) fueron derivados a potenciales evocados auditivos de tronco cerebral. Treinta y cinco recién nacidos (4,39%) presentaron diagnóstico de hipoacusia, 18 (51,43%) hipoacusias de transmisión, 17 (48,57%) hipoacusias neurosensoriales y de estos 3 con hipoacusia profunda bilateral. La asociación a otro factor de riesgo se presenta en la mitad de los niños estudiados, siendo el más frecuente la exposición a ototóxicos.

**Conclusiones:** El porcentaje de niños con diagnóstico de hipoacusia neurosensorial entre los recién nacidos con hiperbilirrubinemia al nacer es superior a la esperada en la población general. De los diagnosticados de hipoacusias neurosensoriales ninguno presentó niveles de bilirrubina indirecta en sangre ≥20 mg/dl, el 47% tenían solo la hiperbilirrubinemia al nacer como factor de riesgo mientras que el 53% evidenciaba otro factor de riesgo auditivo asociado.

© 2014 Elsevier España, S.L.U. and Sociedad Española de Otorrinolaringología y Patología Cervico-Facial. Todos los derechos reservados.
diagnosis and follow-up using evoked auditory potentials in the brain stem (EAPBS).

Version 20.0 for Windows of the SPSS package was used for statistical processing. To study possible associations between category variables Fisher’s exact test was used \( (P<.05) \) or the \( P \) value obtained by Pearson’s Chi squared test \( (P<.001) \).

The study was approved by the Clinical Trials Committee of the Complejo Hospitalario Universitario Insular Materno-Infantil, Gran Canaria.

### Results

During the period from 1 January 2007 to 31 December 2011 a total of 796 NBB were studied. The main risk factor they presented was hyperbilirubinemia, of which 475 (59.67%) were boys and 321 (40.33%) were girls.

Table 1 shows the statistics that describe the distribution of risk factors according to sex.

In the first phase of the Program for the Early Detection of Childhood Hearing Loss transitory evoked otoacoustic emissions were negative in 16.54% of NBB, while in 49.05% of the sample in the second phase evoked transitory otoacoustic emissions were absent. One hundred and five NBB were referred to the EAPBS, 116 boys (14.57%) and 69 girls (8.67%). A total of 93 children did not attend evaluation with EAPBS, of which 54 (29.19%) were boys and 39 (21.08%) were girls.

Regarding the distribution of risk factors for hearing loss shown by the results of the EAPBS, we found that of the 92 NBB who attended this test, of those who had only presented hyperbilirubinemia at birth as a risk factor, 14 were found to have hearing loss while 31 had normal hearing (Table 2).

The distribution of the type of right/left ear hearing loss shown by EAPBS is shown in Table 3; of the 92 patients who were tested, 4 presented left unilateral transmission hearing loss (THL), 13 bilateral THL, 2 right THL and NSHL of the right ear and one unilateral THL of the right ear. Likewise, 10 patients presented bilateral NSHL, one unilateral NSHL of the right ear and one of the left ear, and in 3 patients THL of the right ear was detected together with left ear NSHL.

Table 4 shows the distribution of the figures for total blood bilirubin according to weeks of gestation and sex, while the study of the association between exchange transfusion and sex is shown in Table 5.

When we studied the association between presence of hearing loss detected by EAPBS, total bilirubin in the blood and weeks of gestation, it was found that 11 (45.83%) of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Description of Risk Factor Distribution According to Sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
</tr>
<tr>
<td>Only Hb</td>
<td>255</td>
</tr>
<tr>
<td>Only ototoxic</td>
<td>113</td>
</tr>
<tr>
<td>Only LW</td>
<td>10</td>
</tr>
<tr>
<td>Only others</td>
<td>18</td>
</tr>
<tr>
<td>Hb+otot.+BP+other</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>475</td>
</tr>
</tbody>
</table>

Hb: hyperbilirubinemia; LW: low weight; otot: ototoxic medication.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Distribution of Risk Factors for Hearing Loss Shown by EAPBS.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Only hyperbilirubinemia</td>
<td>31</td>
</tr>
<tr>
<td>Only ototoxic</td>
<td>6</td>
</tr>
<tr>
<td>Only very low weight</td>
<td>0</td>
</tr>
<tr>
<td>Only others</td>
<td>1</td>
</tr>
<tr>
<td>Hyperbilirubinemia+ ototoxic med.+very low weight+others</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
</tr>
</tbody>
</table>

![Figure 1](https://example.com/figure1.png)

Figure 1 Flow diagram used in the Early Detection Program for Childhood Hearing Loss in the Complejo Hospitalario Universitario Insular Materno Infantil de Gran Canaria.
The Relationship Between Neonatal Hyperbilirubinemia and Sensorineural Hearing Loss

Table 3  Distribution of Hearing Loss Type in Right/Left Ear Shown by EAPBS.

<table>
<thead>
<tr>
<th>Left ear EAPBS</th>
<th>Right ear EAPBS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Transmission hearing loss</td>
</tr>
<tr>
<td>Normal</td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>Transmission hearing loss</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Neurosensory hearing loss</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Did not attend</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 4  Description of Total Blood Bilirubin (TB) According to Weeks of Gestation and Sex.

<table>
<thead>
<tr>
<th>Sex</th>
<th>TB values (mg/dl)</th>
<th>Preterm (&lt;37 weeks)</th>
<th>Term (&gt;37 weeks)</th>
<th>Total</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recount %</td>
<td>Recount %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys 5–13.99</td>
<td>124</td>
<td>15.58</td>
<td>42</td>
<td>166</td>
<td>20.85</td>
</tr>
<tr>
<td>14–19.99</td>
<td>115</td>
<td>14.45</td>
<td>130</td>
<td>245</td>
<td>30.78</td>
</tr>
<tr>
<td>≥20</td>
<td>19</td>
<td>2.39</td>
<td>45</td>
<td>64</td>
<td>8.04</td>
</tr>
<tr>
<td>Girls 5–13.99</td>
<td>83</td>
<td>10.43</td>
<td>32</td>
<td>115</td>
<td>14.45</td>
</tr>
<tr>
<td>≥20</td>
<td>13</td>
<td>1.63</td>
<td>40</td>
<td>53</td>
<td>6.66</td>
</tr>
<tr>
<td>Total</td>
<td>427</td>
<td>53.65</td>
<td>369</td>
<td>796</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 5  Study of the Association Between Exchange Transfusion and Sex.

| Sex        | Exchange transfusion | Value of P
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>%</td>
</tr>
<tr>
<td>Boys</td>
<td>11</td>
<td>61.11</td>
</tr>
<tr>
<td>Girls</td>
<td>7</td>
<td>38.89</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>2.27</td>
</tr>
</tbody>
</table>

a  Value of P obtained by Fisher's exact test.

patients presented values of total bilirubin in the blood of from 14 to 19.99 mg/dl, and with fewer than 37 weeks of gestation. Five (45.45%) patients presented the same values after more than 37 weeks of gestation and had hearing loss. A total of 4 (36.36%) of children with total values of bilirubin in the blood above 20 mg/dl and more than 37 weeks of gestation were also diagnosed with hearing loss (P<.001) (Table 6).

Table 6 Study of the Association between the Level of Total Blood Bilirubin, Weeks of Gestation and the Presence of Hearing Loss Detected by EAPBS (P<.001*).

<table>
<thead>
<tr>
<th>Hearing loss</th>
<th>Weeks gestation</th>
<th>Level of bilirubin in mg/dl</th>
<th>Recount</th>
<th>%</th>
<th>Recount</th>
<th>%</th>
<th>Recount</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Preterm (&lt;37 weeks)</td>
<td>13</td>
<td>54.17</td>
<td>11</td>
<td>45.83</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term (&gt;37 weeks)</td>
<td>2</td>
<td>18.18</td>
<td>5</td>
<td>45.45</td>
<td>4</td>
<td>36.36</td>
<td></td>
</tr>
<tr>
<td>[2,0]No</td>
<td>Preterm (&lt;37 weeks)</td>
<td>23</td>
<td>60.53</td>
<td>13</td>
<td>34.21</td>
<td>2</td>
<td>5.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term (&gt;37 weeks)</td>
<td>2</td>
<td>10.53</td>
<td>10</td>
<td>52.63</td>
<td>7</td>
<td>36.84</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>43.47</td>
<td>39</td>
<td>42.40</td>
<td>13</td>
<td>14.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Value of P obtained by Pearson’s Chi-squared test.
The percentage of children studied who were diagnosed deep NSHL of the 796 NBB with hyperbilirubinemia stands at 2.135%. This is higher than the expected percentage of hearing loss in the general population (P<.001), a datum that is statistically significant.

Discussion

It has been demonstrated that the only reasonable strategy for the early detection of hearing loss in childhood is universal early testing.3-8

Severe jaundice that requires exchange transfusion is now relatively rare; nevertheless, moderate hyperbilirubinemia is observed in approximately 60% of newborn babies at term and in 80% of preterm babies. It is accepted that levels of bilirubin in serum >20 mg/dl increase the risk of neurological damage in babies born at term, although it is also admitted that preterm babies may suffer consequences at far lower figures. There is scientific evidence that shows that neurosensory effects are the result of the increase of indirect bilirubin in the blood. Nevertheless, the reason for this has not been proven, given that there is no proportional relationship with the levels of the same. This effect is attributed to the interrelationship with other risk factors that are present in the newly born and which may amplify the effect of hyperbilirubinemia (prematurity, low birth weight, hypoxia, metabolic acidosis or perinatal infections).9-15

The toxicity caused by hyperbilirubinemia may be clinically reversible, and it may either not be expressed or be expressed in very subtle or late manifestations. The study by Suresh and Lucey found no case of hearing loss in spite of prolonged exposure to high levels of bilirubin, >de 20 mg/dl in the majority of cases. This led them to state that bilirubin is not as toxic for the auditory system as is supposed.16 These results coincide with those of our sample, where of the 17 children diagnosed NSHL none were found with levels of indirect bilirubin >20 mg/dl.

Very low birth weight and prematurity are often concomitant, and it is hard to completely separate the factors which are linked to one or the other; these children form the population at greatest risk of NSHL. In these patients concentrations of bilirubin >14 mg/dl represent a risk of hearing loss in 30% of cases.17-18

In our sample, when studying the association between weeks of gestation and hearing loss, we found that of the 35 (38.04%) children diagnosed with hearing loss, 24 (68.57%) were preterm babies (<37 weeks) and 11 (31.43%) were born at term (>37 weeks).

Hyperbilirubinemia is a risk factor for neurosensory deafness, as defined by the Joint Committee on Infant Hearing and the Commission for the Early Detection of Childhood Hearing Loss, and “Hyperbilirubinemia that requires exchange transfusion” is unclear and ambiguous as a specific clinical entity, given that it does not define the level of bilirubinemia that would indicate the need for this technique.19-21

Eighteen exchange transfusions were performed in our series, with blood bilirubin levels of >14 mg/dl. None of these cases suffered severe NSHL, and this datum coincides with Wong et al., who in their study of 99 NBB with jaundice, described 3 cases of exchange transfusion with unaltered EAPBS results.22

Ohl et al. found that associations of 2 or more risk factors significantly increased bilateral hearing loss.23 In our sample, of the 35 NBB diagnosed NSHL, 8 presented hyperbilirubinemia as the sole risk factor, and of these 3 (8.57%) were diagnosed bilateral NSHL and 5 (14.28%) unilateral NSHL. In 27 NBB from 2 to 4 risk factors were present, and the most frequent association was ototoxic medication and low birth weight.

The rate of NSHL among the children who presented associated risk factors in our sample amounted to 2.13%; this datum coincides with that from the studies by Ptok24 and Erenberg et al.,25 which state that the rate of NSHL among children who have an associated risk factor stands at 1%-2%.

In our sample, of the 3 NBB diagnosed NSHL, only one had hyperbilirubinemia as the single risk factor, while in the other 2 this was associated with ototoxic medication and low birth weight.

Conclusions

The percentage of children diagnosed NSHL among NBB with hyperbilirubinemia as a neonatal risk factor is higher than the expected percentage of hearing loss in the general population (P<.001).

Forty-seven percentage of the children diagnosed NSHL only had hyperbilirubinemia at birth as the risk factor for hearing loss, while in the remaining 53% this was associated with another risk factor; none of them required exchange transfusion to treat their neonatal hyperbilirubinemia.

Conflict of Interests

The authors declare they have no conflict of interests.

References