

Incidence of Hypoacusia Secondary to Hyperbilirubinaemia in a Universal Neonatal Auditory Screening Programme Based on Otoacoustic Emissions and Evoked Auditory Potentials

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Introduction: Hyperbilirubinaemia is a neonatal risk factor that has been proved to be associated with sensorineural hearing loss. A high concentration of unconjugated bilirubin place newborn children at risk of suffering toxic effects, including hypoacusia.

Objectives: Review of the newborn screening results with a diagnosis of pathological hyperbilirubinaemia as part of a hearing-loss early detection protocol in the general population based on otoacoustic emissions and evoked potentials.

Material and method: Retrospective study of 21 590 newborn children screened between 2002 and 2006. The selection criteria for defining pathological hyperbilirubinaemia were bilirubin concentrations in excess of 14 mg/dL in pre-term infants and 20 mg/dL in full-term babies. The Universal Neonatal Hearing Screening Programme is a 2-phase protocol in which all children are initially subjected to a transient otoacoustic emissions test (TOAE). Children presenting risk factors associated with auditory neuropathy were always given brainstem auditory evoked potentials (BAEP).

Results: The patients identified as having severe hyperbilirubinaemia in the neonatal period numbered 109 (0.5%) and 96 of these (88.07%) passed the otoacoustic emissions test at the first attempt and 13 (11.93%) did not; 11 of the 13 children in whom the otoacoustic emissions test was repeated passed it successfully. The 2 children who failed to pass the otoacoustic emissions test had normal BAEP results; 3 (2.75%) of the newborn infants who passed the TOAE test did not pass the BAEP.

Discussion: Hyperbilirubinaemia values previously considered safe may harm the hearing system and give rise

Incidencia de hipoacusia secundaria a hiperbilirrubinemia en un programa de cribado auditivo neonatal universal basado en otoemisiones acústicas y potenciales evocados auditivos

Introducción: La hiperbilirrubinemia es un factor de riesgo neonatal que tiene probada asociación con la hipoacusia neurosensorial. Una concentración elevada de bilirrubina no conjugada pone al neonato en situación de riesgo de efectos tóxicos, entre los que se encuentra la hipoacusia.

Objetivos: Revisión de los resultados del cribado de neonatos con diagnóstico de hiperbilirrubinemia patológica dentro de un protocolo de detección precoz de la hipoacusia en la población basado en otoemisiones y potenciales evocados.

Material y método: Estudio retrospectivo de 21.590 neonatos cribados entre 2002 y 2006. Los criterios de selección para definir hiperbilirrubinemia patológica fueron las concentraciones de bilirrubina mayor de 14 mg/dl en el pretérmino y 20 mg/dl en el neonato a término. El Programa de Cribado Auditivo Neonatal Universal es un protocolo de dos fases en el que inicialmente todos los niños se someten a un test de otoemisiones acústicas transitorias (OEAT). A los niños que presentan factores de riesgo asociados a la neuropatía auditiva siempre se les realiza potenciales evocados auditivos de tronco cerebral (PEATC).

Resultados: Se identificó a 109 (0,5 %) pacientes con hiperbilirrubinemia severa en el período neonatal, 96 (88,07 %) de ellos superaron la prueba de otoemisiones en el primer intento y 13 (11,93 %) no pasaron; 11 de los 13 niños a quienes se repitió la prueba de otoemisiones la superaron. En los 2 niños que no superaron las otoemisiones acústicas los PEATC fueron normales; 3 (2,75 %) neonatos que pasaron la prueba de OEAT no superaron los PEATC.

Discusión: Los valores de hiperbilirrubinemia previamente considerados seguros pueden dañar el sistema auditivo y ocasionar problemas aislados en el procesamien-

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to isolated problems in auditory processing without being associated with other signs of classical kernicterus. Our results show that hyperbilirubinaemia-related auditory neuropathy reveals changes over time in the audiometric outcomes.

Key words: Hypoacusia secondary to hyperbilirubinaemia. Neonatal screening programme. Otoacoustic emissions. Evoked auditory potentials.

to auditivo sin asociarse a otros signos del kernicterus clásico. Nuestros resultados indican que la neuropatía auditiva en relación con la hiperbilirrubinemia muestra cambios en los resultados audiométricos con el tiempo.

Palabras clave: Hipoacusia secundaria a hiperbilirrubinemia. Cribado auditivo neonatal. Otoemisiones acústicas. Potenciales evocados auditivos.

INTRODUCTION

Hyperbilirubinaemia is a neonatal risk factor clearly associated with sensorineural hearing loss. Severe jaundice requiring extracorporeal blood transfusion has nowadays become quite rare; however, moderate hyperbilirubinaemia is seen in some 60% of neonates born at term and in 80% of pre-term newborns during the first week of life due to shorter half-life of red blood cells and immature liver function.¹ Bilirubin is made from the degradation of red blood cells that then undergo metabolism in the liver. In serum, bilirubin presents in 2 forms: indirect or non-conjugated bilirubin and direct bilirubin that, after being conjugated with glucuronic acid, is quickly excreted. Non-conjugated bilirubin can cross the brain-blood barrier and accumulate on the brainstem auditory pathway; as a result, high concentrations of indirect bilirubin close to or above 20 mg/dL put the neonate at risk for its toxic effects, including hearing loss. This risk is increased if associated with other factors such as perinatal hypoxia and prematurity, which increase permeability of the brain-blood barrier and cell membrane to bilirubin. Damage to the auditory pathways consists of neuropathy or auditory dys-synchrony and other impairments of audiological processing that may present in children with or without other associated signs of classical kernicterus, a syndrome arising from the binding of bilirubin to the basal ganglia of the central nervous system including cerebral palsy, athetosis, hearing loss, and intellectual disability.

Given the location of bilirubin-induced neurological damage, neonatal hearing loss screening programmes based on otoacoustic emissions should contemplate the possibility of false negatives. Given that otoacoustic emissions reflect the status of external ciliary cell function, a child with auditory neuropathy may exhibit normal responses on testing with otoacoustic emissions, whereas if he/she undergoes brainstem evoked auditory potentials, the auditory nerve function fails to appear or is altered. Thus, the retrocochlear injury caused by hyperbilirubinaemia, which leaves the cochlea intact, makes it impossible to detect in a screening protocol based exclusively on otoacoustic emissions. In order to guarantee that the auditory neuropathy is identified as much as possible, the combined use of otoacoustic emissions (OAE) and brainstem evoked auditory potentials (BEAP) is recommended for screening protocols in high-risk neonates. The association of BEAP and OAE reflects preneural and neural functioning of the auditory system and currently constitutes the most sensitive combination of tests available.²

We present a retrospective review of the results of the neonatal screening programme in children with a diagnosis of hyperbilirubinaemia as the only or main risk factor for auditory neuropathy, within a protocol of a universal neonatal hearing screening programme based on the combined use of transient OAE (TOAE) and BEAP.

MATERIAL AND METHOD

Participants

A retrospective review is made of 21 667 neonates screened between June 2002 and March 2006, within a programme for attention to childhood hearing deficit promoted by the Regional Government of Asturias. The neonates selected presented hyperbilirubinaemia as the only or main risk factor for auditory neuropathy. The selection criterion used to define significant hyperbilirubinaemia was the finding of maximum values of total serum bilirubin greater than 14 mg/dL in preterm children and 20 mg/dL in children born at term during the neonatal period. Cases displaying liver disease or cholestasis were excluded.

Screening Protocol

The Universal Neonatal Hearing Loss Screening Programme consists of a protocol based on the combined use of TOAE and BEAP, in which all children are initially screened by means of TOAE. Those who fail the TOAE on 3 successive attempts (2 days, 15 days, and 3 months after birth) are sent for BEAP testing and subsequent full diagnostic work-up if hearing loss is confirmed. Children who present risk factors for auditory neuropathy, such as family history, perinatal hypoxia-ischaemia, and hyperbilirubinaemia always undergo TOAE followed by BEAP in order to guarantee that no retrocochlear hearing loss goes undetected.

Transitory Otoacoustic Emissions

TOAE testing is performed using the Capella cochlear emissions analyser (GN Otometrics, Copenhagen, Denmark) operated by a laptop computer. An experienced nurse conducted the evaluations in all cases just before the children were released from hospital, taking advantage of physiological postprandial sleepiness. Once the proper placement of the probe and adequacy of the stimulus has been checked, TOAE testing is carried out in accordance with the established standards.^{3,4} The results are categorized as "pass" or "fail."

Brainstem Evoked Auditory Potentials

BEAP tests are performed following a standard protocol with EP-15 commercial instrumentation (Interacoustics, Assens, Denmark) if the neonate had not passed the TOAE or else with the Echo-Screen AABR (Fischer-Zoth Diagnosesysteme GmbH, Germany) when TOAE testing results were normal. The electrodes are placed on the central vertex (Cz), the forehead (Fpz), and right and left mastoid processes (M1 and M2). Inter-electrode impedances are kept below 5 k Ω . The right and left ears are studied separately by means of in-the-ear headphones with alternating 0.1-ms clicks, presented at a rate of 49.1 stimuli/s for threshold determination. An average of 2000 sweeps was taken using 50 to 1500 Hz filters. The initial stimulus is presented at 60 dB nHL and is later lowered or raised in 10 dB nHL increments until the V-wave threshold is found. The result is considered normal if the V-wave is stimulated at 30 dB nHL or less.

Audiometry

The audiological diagnosis includes threshold determinations for the different frequency bands by means of methods appropriate to each patient's age and behavioural characteristics: behaviour observation audiometry and conditioned response to sound (conditioned orientation reflex and visually cued audiometry).

RESULTS

Our Universal Neonatal Hearing Loss Screening Programme currently covers 95.68% of all newborns in the Region of Asturias. Of the 21 590 neonates screened, 2191 (10.1%) failed to pass the initial test. Of these, 284 children did not pass TOAE testing in 1 or both ears on the third attempt; hence, they were given an appointment for BEAP testing which detected significant hearing loss in 108, representing 0.50% (5/1000) of all the neonates screened.

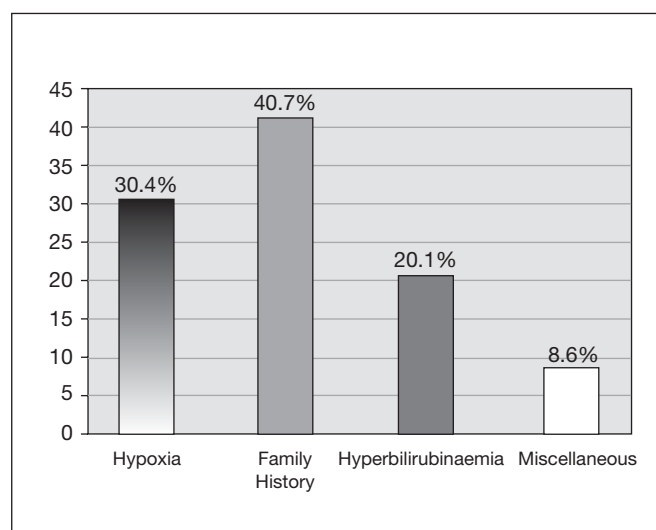


Figure. Retrocochlear risk factors: 496 (23/1000).

Risk Factors

Of the 21 590 neonates screened, the presence of risk factors for retrocochlear hearing loss were detected in 496 (23/1000): perinatal hypoxia in 151, family history in 202, hyperbilirubinaemia in 100, and 2 or more factors in 43 (Figure).

The 109 patients (52 females and 57 males) with hyperbilirubinaemia in the neonatal period as the only or main risk factor for retrocochlear hearing loss account for 0.50% of all the newborns. The maximum mean total serum bilirubin concentration was 18.21 (2.98) mg/dL (maximum, 26.8 mg/dL).

Of the 109 patients with neonatal hyperbilirubinaemia as the only or main risk factor for retrocochlear hearing loss, perinatal hypoxia-ischaemia was also identified in 9 (Apgar score of less than 5 at 1 minute or at 5 min.).

Of the 109 children, 73 were admitted into the neonatal intensive care unit for a mean 12.2 days; 11 presented prematurity of 32 weeks or less (mean, 35 [3] weeks) and 6 neonates weighed less than 1500 g (mean, 2660 [743]). Not a single neonate with a family history of hearing loss was detected. Treatment for hyperbilirubinaemia consisted of phototherapy for a minimum of 48 h and a maximum of 10 days (mean, 3.87 [1.6] days). In 1 case, extracorporeal transfusion was associated.

Transient Otoacoustic Emissions

Of the 109 children with hyperbilirubinaemia screened, 96 passed the test (88.07%) and 13 failed (11.93%); 11 of these 13 neonates passed when TOAE testing was repeated and 2 (1.8%) were unable to pass it and were therefore given an appointment for BEAP testing.

Brainstem Evoked Auditory Potentials

The 2 neonates who failed to pass the screening with TOAE exhibited normal BEAP results.

In 3 children who displayed normal TOAE results, the BEAP test results were abnormal (2.75%): 1, with a total bilirubin level of 17.1 mg/dL, failed to respond to the BEAP on 2 attempts and hearing loss was confirmed in the subsequent audiometric evaluation. A significant improvement in hearing was confirmed clinically at the subsequent check-ups (subjective or behavioural audiometric methods) and borderline and later normal hearing levels were achieved at all frequencies (20-40 dB). In the second child (total bilirubin concentration, 14.8 mg/dL), significant unilateral hearing loss was identified on the BEAP (threshold of 70 dB) with improvement after 2 months (threshold, 50 dB). The third child (total bilirubin concentration, 17.3 mg/dL) also exhibited significant unilateral hearing loss (threshold, 50 dB), with subsequent spontaneous improvement seen on the test performed 2 months after the first (threshold, 40 dB). The 3 patients achieved stable audiometry at 18 months of age.

DISCUSSION

The advances made in medical treatments have significantly lowered the incidence and severity of kernicterus

in the neonate born at term; however, the toxic effects of moderate concentrations of bilirubin on the nervous system of pre-term neonates or those with low birth weight may be related to the appearance of auditory neuropathy.

Hyperbilirubinaemia is associated with sensorineural hearing loss and auditory neuropathy, which is clinically defined by the absence or alterations on BEAP in a context of normal otoacoustic emissions, which implies normal peripheral auditory function, but damage or dysfunction in the nerve or in the brainstem auditory pathway.

TOAE has gained acceptance as a screening tool given its advantages as a fast, reliable, and inexpensive test compared to BEAP. However, otoacoustic emissions are limited in the evaluation of hearing in hyperbilirubinaemic neonates.⁵ In these patients there is concern regarding false negatives, as occurs in the case of auditory neuropathy or auditory dys-synchrony.

If a neonatal hearing loss screening programme chooses otoacoustic emissions as the only tool by which to study neonates with hyperbilirubinaemia, 13% of cases will go undetected. Therefore, the combined use of BEAP and OAE is recommended for screening for neonatal hearing loss in cases with hyperbilirubinaemia.⁶

There are important hindrances to the practical implementation in Spain of the specifications of risk factors from the JCIH⁷ and CODEPEH⁸ (Commission for the early detection of infantile hearing loss), given that there is often no clear clinical definition and treatment intervention on some of the factors has moved forward to the point that their impact may no longer be the same. "Severe hyperbilirubinaemia requiring extracorporeal blood transfusion" is not only an ambiguous clinical definition, but the treatment for neonatal jaundice has changed. The serum bilirubin value at which extracorporeal blood transfusion is indicated is not defined, so this clinical variable is subject to many interpretations. Moreover, extracorporeal blood transfusions are currently rare, thanks to the advent of aggressive treatment with phototherapy.⁹

Hyperbilirubinaemia figures previously thought to be safe may actually be harmful for the auditory system and cause isolated alterations in auditory processing, without being associated with other signs of classical kernicterus.¹⁰ In order to respond to this, our universal neonatal screening programme set total serum bilirubin concentrations of 14 mg/dL in pre-term infants and 20 mg/dL in infants born at term as the criteria for performing BEAP plus TOAE, despite normal results on the TOAE.

The incidence of minor effects due to bilirubin is unknown. Madden et al¹¹ found that 50% of their cases of auditory neuropathy had a history of hyperbilirubinaemia and that some patients present temporary hearing loss that resolved spontaneously. Hyperbilirubinaemia causes jaundice when serum bilirubin reaches concentrations of 23 mg/dL. Jaundice is observed in some 60% of neonates born at term and in 80% of pre-term neonates. The toxic effects of elevated indirect bilirubin serum concentrations, including hearing loss, are boosted when associated to perinatal hypoxia-ischaemia and prematurity, through an

increase in nerve cell susceptibility.¹ Sensorineural involvement appears as a result of the increase of indirect bilirubin in blood, but is not proportionally related to the values it reaches; hence, it is possible to find cases with involvement and 8 mg/dL of bilirubin and normal cases with 25 mg/dL of bilirubin. This effect may be due to the interaction with other risk factors present in the neonate that may enhance the effect of the hyperbilirubinaemia (prematurity, low birth weight, hypoxia, metabolic acidosis, or perinatal infections). In these patients, bilirubin concentrations greater than 14 mg/dL represent a risk of hearing loss in 30% of the cases.¹² The work by Suresh et al¹³ is of interest: a study of 42 patients with Crigler-Najjar's syndrome, in which not a single case of hearing loss was found despite prolonged exposure to high bilirubin concentrations in excess of 20 mg/dL in most cases, leading them to point out that bilirubin is not as toxic for the auditory system as previously thought. On the other hand, Newman et al,¹⁴ in a prospective, multicentric study that collected the data on 41 324 newborns weighing more than 2500 g, did not find any association between sensorineural hearing loss and hyperbilirubinaemia.

The physiopathology of hearing loss caused by hyperbilirubinaemia is not perfectly defined, although its toxicity can affect the cochlea, the auditory nerve, and the brainstem.¹⁵⁻¹⁷ Bilirubin selectively injures the auditory nuclei of the brainstem and the spiral ganglion containing the bodies of the first neurons of the auditory pathway. The inner ear appears to be spared.¹⁸ The mechanism of bilirubin's neurotoxicity and risk values are currently unknown, but it is assumed that it must cross the brain-blood barrier in order to exert a later neurotoxic action boosted by other metabolic disorders such as acidosis, hypoxia, hypercapnia, or hyperosmolarity.¹⁹ In vitro studies have revealed a series of alterations associated with hyperbilirubinaemia, such as energy metabolism modification, cell membrane morphological, and functional injury, alteration of intracellular enzymes, inhibition of DNA and protein synthesis, and alteration of neurotransmitter synthesis. In a murine model of auditory neuropathy due to hyperbilirubinaemia, lesions were found in the spiral ganglion and selective damage of the long, myelinated nerve fibres of the auditory nerve, without findings of alterations of the ciliary cells of the cochlea.²⁰

In our series, the incidence of hyperbilirubinaemia greater than the values defined for indicating BEAP in the children screened with otoacoustic emissions is 0.5% (5/1000 neonates). Three cases were detected of neonates with normal otoacoustic emissions who exhibited altered BEAP test results. Out of 21 590 children, we are only aware of 1 case that required extracorporeal blood transfusion and that did not present alterations on OAE testing nor on the BEAP. Wong et al's series²¹ found 3 cases of extracorporeal blood transfusion in 99 neonates with jaundice and unaltered BEAP. Thus, in our experience, the current definition of hyperbilirubinaemia as a risk factor would have left cases with hearing involvement undetected, ie, false negatives in the screening programme.

Neurotoxicity reversibility has been observed in experimental as well as clinical models, but the protective mechanisms of the cell against the toxicity of bilirubin are unknown, as well as whether prolonged exposure causes permanent neural alteration. There is controversy as to the point at which the auditory pathway is damaged, the typical fall in high-pitch tones points toward greater susceptibility to cell damage caused by these frequencies in the cochlear nuclei. Cochlear function is intact due to the presence of otoacoustic emissions in the affected patients; however, involvement of the auditory pathway is demonstrated by BEAP, a test that is currently the most widely used in these children to demonstrate both this complication, as well as to reveal its reversibility after bilirubin figures decrease following treatment. Hearing loss varies depending on nerve involvement, which may run from mild to profound, with a fall in high-pitch tones; it may be reversible or remain stable over time, and other cases may develop late-onset progressive hearing loss.²² Our findings also indicate that auditory neuropathy associated with hyperbilirubinaemia shows changes in audiometric outcomes over the course of time. Madden et al¹¹ report that 9 out of 18 children with severe or profound hearing loss had a spontaneous improvement in hearing between the first and fifteenth month after diagnosis. This tendency toward spontaneous improvement or resolution in hearing loss caused by neonatal hyperbilirubinaemia has also been documented by Rhee et al⁵ and Wong et al,²¹ who found 9 children with BEAP alterations among 99 neonates born at term with non-haemolytic hyperbilirubinaemia. With the exception of 2 cases, all recovered normal thresholds prior to 2 years of age. Appropriate treatment of jaundice before the development of kernicterus accounts for the children's improvement in hearing thresholds. However, it must be remembered that patients diagnosed with auditory neuropathy tend to present worse word intelligibility than expected given their audiometric thresholds; hence, audiological improvement in these children may not be reflected in their development as would otherwise be expected. Many patients will be found to have difficulties in understanding words, particularly if there is noise. It is therefore important to remind relatives and paediatricians that having passed the hearing tests included in the neonatal hearing loss screening programme does not eliminate the need to monitor language development systematically and consistently and to conduct hearing screening in school-aged children.

CONCLUSIONS

1. The current definition of neonatal hyperbilirubinaemia as a risk factor is not enough to prevent false negatives in a screening programme based on otoacoustic emissions.

2. The use of otoacoustic emissions as the only screening tool in neonates with jaundice is inappropriate. BEAP should be added in order to avoid false negatives.

3. With the serum bilirubin values considered as the risk criterion for hearing loss in our experience (14 mg/dL in pre-term infants and 20 mg/dL in infants born at term), a 0.5% incidence rate can be expected, which translates into performing 5 BEAP per 1000 newborns, in order to detect 2.75% cases of hearing loss.

4. In auditory neuropathy caused by hyperbilirubinaemia, auditory thresholds tend to improve spontaneously during the first 2 years of life.

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