Auditory evoked potentials in children at neonatal risk for hypoacusis[1]

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ABSTRACT *Brainstem auditory evoked potentials provide a simple, noninvasive method of evaluating hearing function and have been widely used for early detection of hypoacusis in children. Between April 1992 and May 1994, a study was done of 400 Mexican children who presented at least one neonatal risk factor for hearing impairment. The average age of the children studied was 6.6 months and their average gestational age at birth was 35.1 weeks. Just over half of the children had been treated with amikacin. The study found 1 427 risk factors (about 3.5 per child), the most common ones being exposure to ototoxic substances, hyperbilirubinemia, and birthweight <1 500 g. In 27% of the children, peripheral auditory changes were found, and 13% did not respond to auditory stimuli. Low birthweight and young gestational age at birth, high serum concentration of bilirubin, sepsis, subependymal or intraventricular hemorrhage, mechanical ventilation, and exposure to ototoxic substances were significantly associated with the presence of severe or profound hypoacusis.*

The auditory evoked potentials of the brain stem afford a simple, noninvasive way of evaluating the hearing function. For this reason, a test of these potentials is very often used for early detection of hypoacusis and neural conduction irregularities in the auditory pathways of children (*1*). The technique does not require the cooperation of the patient and is easily reproducible (*2, 3*). Initial auditory responses in neonates appear in the 26th and 27th weeks of pregnancy (*4, 5*). Progressively over time, these follow a "maturation pattern" in which interwave intervals and latencies decrease and the amplitudes of the brainstem auditory evoked potentials increase (*6*).

The usefulness of this test for detecting auditory irregularities in newborns has been demonstrated in cases of prematurity (*7*), bacterial meningitis (*8*), hyperbilirubinemia (*9*), neonatal asphyxia (*10*), and prenatal exposure to lead (*11*). If risk factors for neonatal auditory irregularities are present, the test is deemed indispensable (*12*).

The purpose of the study reported here was to describe the type and frequency of irregularities in brainstem auditory evoked potentials within a population of 400 Mexican children with at least one neonatal risk factor for hypoacusis (Table 1).

MATERIALS AND METHODS

Between April 1992 and May 1994, a study was conducted of the evoked potentials of 800 ears in 400 children who met the following eligibility criteria: having been born at the National Institute of Perinatology in the Federal District, residing in the Valley of Mexico (the metropolitan area of Mexico City), having at least one neonatal risk factor for hypoacusis (*12*), and participating by agreement in the Project to Detect Neuropsychologic Irregularities of Perinatal Origin *(Proyecto de Detección de Alteraciones Neuropsicológicas de Origen Perinatal—PDANDOP)*. The study group included some children born before April 1992 who were

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TABLE 1. Risk factors for hypoacusis in neonates

Family history of congenital hypoacusis
Congenital perinatal infection (with toxoplasma, rubella, cytomegalovirus, herpesvirus, and others)
Malformations of the head and neck
Birthweight <1 500 g
Hyperbilirubinemia with signs indicating blood transfusion
Exposure to ototoxic drugs
Bacterial meningitis
Apgar score of <3
Assisted ventilation for more than 10 days
Suspicion of syndromes associated with hypoacusis (Waardenburg, Usher, etc.)
Subependymal or intraventricular hemorrhage
Septicemia

Source: I. Bergman et al. (*12*).

participating in the PDANDOP, had not previously been studied using the evoked potentials test, and satisfied the above eligibility criteria.

All of the children showing abnormal results in the evoked potentials test were enrolled in a monitoring program. In that program, the tests and evaluations were repeated at the conclusion of a three-month period; an assessment of language development was performed; and after the child's third birthday confirmatory hypoacusis tests were conducted using tonal audiometry and speech audiometry. The analysis reported here deals only with the results of the initial evoked potentials testing.

The potentials studied were evoked during physiologic sleep by means of monaural stimulation with clicks of alternating polarity. The stimulation was first applied during a 2-minute period of adaptation preceding the recording that progressively increased in intensity by 30 dB increments until it reached the audible level of 80 dB (audible level, sound pressure of 20 micropascals), at which point averaging was initiated. Each stimulus lasted for 100 microseconds, and the stimuli were repeated 11 times per second.

The clicks were released through TDH-49 earphones in an isolated room especially designed for this purpose. The ear not being tested was masked with white sound 30 dB below the intensity of the stimulus. Cerebral electrical activity was recorded with gold disk electrodes placed at derivations Cz (+), A1, and A2, after cleansing the area with acetone-alcohol and applying conductive gel. The study ear was negative and the subject's other ear was ground (*13*).

The signal coming from the electrodes was kept below 4 kilo-ohms and was used for computer input. The band-pass filters were set between 300 and 3 000 Hz in order to reduce the registering of other biologic signals (electrocardiogram and electromyogram). The time of analysis subsequent to stimulation was 10 milliseconds.

A total of 2 024 stimuli were averaged, and this process was repeated at least once in order to ensure reproducibility of the response. After making the recording, averages were obtained, the intensity of the stimulus being reduced 20 dB at a time until no response was obtained, and then subsequently raised by 10 dB increments until a clear and reproducible visualization of only the V wave (the electrophysiologic threshold) was obtained. A cursor was used to measure the latency of waves I, III, and V. The latency of the interwave intervals was obtained automatically by means of a computer program.

The results of the study were classified in accord with the criteria of Stockard et al. (*14*) (Table 2). In the case of premature children, the corrected postconceptual or gestational age (postnatal age in weeks plus gestational age at birth) was taken into account.

Arithmetic means, standard deviations, and value ranges were used to conduct the statistical analysis. The means were compared using Student's t test (after verifying that the distributions of the variables were normal and the variances homogeneous), while proportions were verified using the chi-square test. The level of statistical significance selected was 0.05.

RESULTS

The arithmetic mean of the study children's age was 6.6 months (range: 1 day to 6 years), with those under 6 months old accounting for 84% of the total. The mean gestational age at birth was 35.1 weeks, with one standard deviation (SD) being ±3.5 weeks and the values ranging from 24 to 42 weeks. Approximately 67% of the study children were born before 37 weeks of gestation. The children's mean birthweight was 2 034 g (SD = 870 g; range = 700–4 575 g), with most children (234) having birthweights under 2 000 g. The mean maximum concentration of indirect serum bilirubin found during admission of the 265 children evaluated for this factor was 13.6 mg/dL (SD = 5.1 mg/dL; range = 1–30 mg/dL). Because neonatal septicemia was suspected, 231 (58%) of the children were given amikacin endovenously, 97 (24%) were given furosemide, and two (0.5%) were given gentamycin.

TABLE 2. Classification of brainstem auditory evoked potentials

1. Normal: When the absolute latencies of waves I, III, and V, and the interwave intervals I–III, III–V, and I–V are found within the interval encompassed by the mean ±2 standard deviations for the patient's age, and the auditory threshold is 35 dB or less.
2. Type I peripheral irregularity: When wave I latency and the auditory threshold are high.
3. Type II peripheral irregularity: When wave I is of low voltage or absent and the auditory threshold is high.
4. Absence of all components. When no component is identified.
5. Absence of late components. When no III or V waves can be identified.
6. Increase in the interwave intervals.

Source: J.E. Stockard et al. (*14*).

A total of 1 427 risk factors were identified (about 3.5 factors per child). In 114 (28%) of the children, only one risk factor was documented, while in 51 (13%) two such factors were identified, and in the rest (59%) three or more were detected (Table 3).

Auditory abnormalities were detected in 45% of the ears studied. Of these, peripheral abnormalities accounted for over half (27.5% of all the ears tested), and absence of all components (in 13.4% of all the ears tested) was very common (Table 4, Figures 1 and 2).

Regarding the various groups at risk of hypoacusis, the highest percentages of children with abnormalities were found in the groups with subependymal or intraventricular hemorrhage (79%), bacterial meningitis (76%), jaundice with blood transfusion (69%), and neonatal sepsis (68%) (Table 5).

In addition, the existence of an inverse relationship was affirmed between gestational age at birth and birthweight, on the one hand, and test results indicating abnormal auditory evoked potentials of the brain stem. By way of example, Figure 3 shows the relationship between gestational age at birth and the frequency of auditory irregularities.

In order to analyze risk factors associated with bilateral absence of all components, children with this test result (designated as Group I, n = 48) were compared to the remaining 352 participants (designated Group II). A significantly higher number of risk factors per child was detected in Group I than in Group II ($\chi^2 = 46.3$; $P < 0.001$). In addition, significant differences were detected between the two groups with regard to birthweight ($t = -3.94$; $P < 0.0001$), gestational age at birth ($t = -4.66$; $P < 0.0001$), maximum concentration of serum bilirubin ($t = -3.25$; $P < 0.001$), use of amikacin ($\chi^2 = 41.90$; $P < 0.001$), use of furosemide ($\chi^2 = 18.80$; $P < 0.01$), bacterial meningitis ($\chi^2 = 31.22$; $P < 0.001$), subependymal or intraventricular hemorrhage ($\chi^2 = 27.66$; $P < 0.001$), and use of mechanical ventilation ($\chi^2 = 26.09$; $P < 0.001$) (Table 6).

TABLE 3. Frequencies of hypoacusis risk factors identified in the study (each study subject could and often did have more than one risk factor); National Institute for Perinatology, Mexico, 1992–1994

Risk factor	*n*
Exposure to aminoglycosides or furosemide	235
Neonatal septicemia	231
Jaundice requiring phototherapy	201
Gestational age <34 weeks	177
Birthweight <1 500 g	155
Apgar score of <3 at 1 minute	134
Assisted ventilation	123
Subependymal or intraventricular hemorrhage	68
Jaundice requiring blood transfusion	46
Congenital perinatal infection (rubella, 12; cytomegalovirus, 2; toxoplasmosis, 1)	15
Bacterial meningitis	13
Prenatal exposure to antiepileptic drugs[a]	9
Prenatal exposure to gentamycin	8
Congenital hydrocephaly	5
Hydranencephaly	3
Colpocephaly	1
Arnold-Chiari syndrome, type 2	1
Prenatal exposure to lead[b]	4
Facio-auricular-vertebral syndrome	2
Auricular malformation	2
Family history of congenital hypoacusis	1
Craniosynostosis	1
Delayed intrauterine growth	1
Family history of sudden death	1
Total	1 427

[a] Proposed study of the effects of prenatal exposure to antiepileptic drugs on brainstem auditory evoked potentials (*23*).
[b] Proposed prospective study of lead in Mexico City (*10*).

TABLE 4. Results obtained from testing the study subjects' 800 ears; National Institute for Perinatology, Mexico, 1992–1994

Findings	No. of ears	%
Normal	438	54.7
Peripheral irregularity I	120	15.0
Peripheral irregularity II	100	12.5
Absence of late components (III and V)	3	0.4
Reduction of the I/V ratio	9	1.1
Increased I–V interval	23	2.9
Absence of all components	107	13.4

DISCUSSION

Children experiencing hearing loss during the initial months of life and whose auditory thresholds are above 65 dB often exhibit defective language development. Successful rehabilitation is directly dependent on early detection and treatment (*4*). The large number of children selected for this study reflects the high frequency of children with risk factors for auditory disorders. Many of these children (in the case of the present study, 90% of the study population) are discharged from specialized neonatal therapy facilities and could benefit from hypoacusis screening prior to reaching 1 year of age.

FIGURE 1. Normal recording of brainstem auditory evoked potentials of a neonate whose mother was infected with rubella during the third trimester of pregnancy (RE = right ear; LE = left ear). The upper lines show the principal waves (I, III, V) at 80 dB, while the lower lines show the electrophysiologic threshold at 30 dB. Horizontal calibration bar = 1 millisecond; vertical calibration bar = 0.16 microvolts (records shown in duplicate to ensure reproducibility)

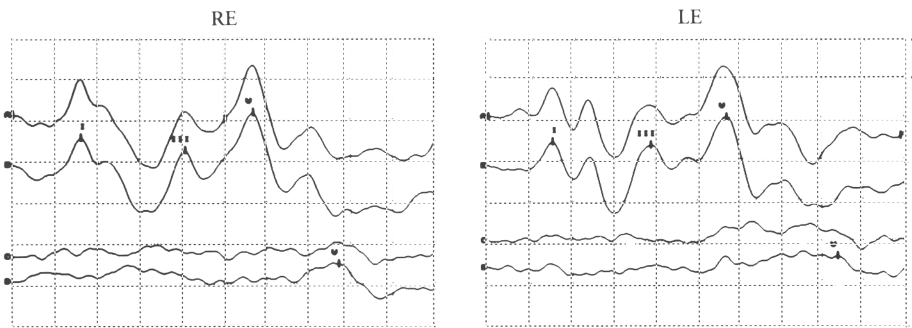


FIGURE 2. Abnormal recording of brainstem auditory evoked potentials of a neonate with multiple risk factors. (RE = right ear; LE = left ear). The lines show an absence of response at 100 dB. Horizontal calibration bar = 1 millisecond; vertical calibration bar = 0.16 microvolts (records shown in duplicate to ensure reproducibility)

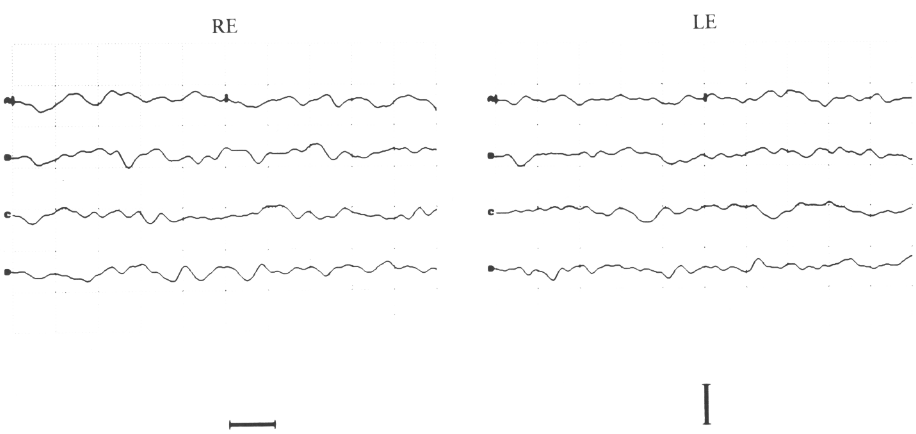
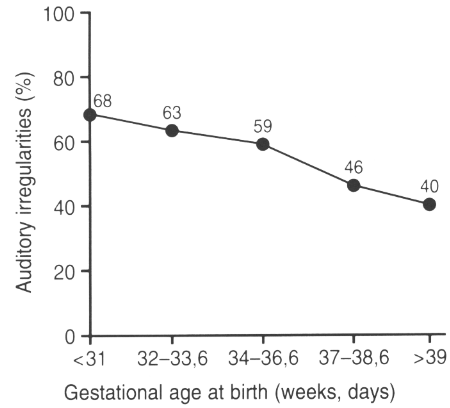


TABLE 5. Frequency of abnormalities and risk factors detected in the 400 study subjects (each subject could and often did have more than one risk factor)

Risk factor	No. of patients	Abnormal test results No.	%
Congenital perinatal infection with toxoplasma, rubella, cytomegalovirus, or herpesvirus	15	9	60
Apgar score of <3 at 1 minute	134	73	54
Blood transfusion	46	31	69
Birthweight <1 500 g	155	104	67
Gestational age at birth <34 weeks	177	116	65
Neonatal sepsis	231	158	68
Bacterial meningitis	13	10	76
Subependymal or intraventricular hemorrhage	68	54	79

FIGURE 3. Relationship between the percentage of auditory irregularities among the study subjects and gestational age at birth



Most of the patients studied were born prior to the 37th week of gestation with a birthweight of less than 2 000 g and required administration of potentially ototoxic drugs (amikacin, furosemide). This helps account for the fact that abnormalities were detected in close to half of the cases tested; the causes documented include cochlear disturbance (in children exposed to furosemide and amikacin) (*15, 16*), tubal dysfunction (in those receiving mechanical ventilation) (*17*), and disturbances of the cochlear nuclei (as a consequence of hyperbilirubinemia and hypoxia) (*17–19*). Also noteworthy is the high frequency of cases in which abnormalities were diagnosed in children who developed subependymal or intraventricular hemorrhage, bacterial meningitis, jaundice, and septicemia—a circumstance accounted for by the effect of these developments on the acoustic nerve (*20*), cochlear hemorrhage (*21*), and exposure to other risk factors (mechanical ventilation, aminoglycosides, etc.).

The inverse relationship found between the frequency of auditory disorders and gestational age/birthweight leads us to assume, in the first place, that immature auditory neurologic pathways are particularly susceptible to such disorders. It is also possible, however, that auditory sequelae are more frequently associated with the increased survival of low birthweight

TABLE 6. Comparison of risk factors possessed by children with bilateral absence of all components of brainstem auditory evoked potentials (Group I) and risk factors possessed by the rest of the study children (Group II). The first three listings under the two groups show the mean values for the group members ± one standard deviation, while the remaining listings show the number of children in each group possessing the risk factor involved

Risk factors	Group I (n = 48)	Group II (n = 352)	P
Birthweight	1 637 ± 721 g	2 087 ± 875 g	<0.0001[a]
Gestational age at birth	33.1 ± 2.9 weeks	35.3 ± 3.5 weeks	<0.0001[a]
Maximum serum concentration of indirect bilirubin	16.5 ± 6 mg/dL	13.1 ± 4.8 mg/dL	<0.001[a]
Apgar score of <3 at 1 minute	17	117	NS[b]
Prenatal congenital infection with toxoplasma, rubella, cytomegalovirus, or herpesvirus	1	14	NS[b]
Phototherapy[c]	30	171	NS[b]
Blood transfusion	12	34	<0.01[b]
Neonatal sepsis	34	191	<0.05[b]
Bacterial meningitis	8	5	<0.001[b]
Use of amikacin	47	170	<0.001[b]
Use of furosemide	25	80	<0.01[b]
Subependymal or intraventricular hemorrhage	21	47	<0.001[b]
Mechanical ventilation	27	86	<0.001[b]
More than three risk factors	42	126	<0.001[b]

[a] Student's t test.
[b] χ^2 test; NS = not significant.
[c] All those receiving blood transfusions were given phototherapy.

neonates exposed to multiple potentially ototoxic factors (*22*).

An absence of potentials recorded at intensities greater than 80 dB above the audible level indicates acute auditory disturbance (*14*). The risk factors statistically associated with this type of abnormality make it possible to construct a high-risk profile for neonates. These risk factors are as follows: low birthweight, low gestational age at birth, acute jaundice, having been given amikacin or furosemide, having undergone mechanical ventilation, subependymal or intraventricular hemorrhage, and bacterial meningitis (*23*).

The statistical association found between a high number of risk factors and the presence of profound hypoacusis suggests that the above-listed risk factors may have a synergistic effect, especially in children of low birthweight and low gestational age at birth. In such children, complications are extremely frequent, and the children tend to remain in the hospital for extended periods. The risk factors identified are observed more and more frequently in children discharged from neonatology wards. Hence, these patients constitute a group at high risk of exhibiting auditory disorders. The social and economic problems posed by children with hypoacusis, care for which requires both technology and personnel specializing in rehabilitation (psychologists, teachers, language specialists), may be important in the future.

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RESUMEN

Potenciales provocados auditivos en niños con riesgo neonatal de hipoacusia

Los potenciales provocados auditivos del tallo cerebral son un método sencillo y no invasor de evaluación de la función auditiva, que se utiliza ampliamente en niños para detectar tempranamente hipoacusia. Entre abril de 1992 y mayo de 1994, se estudiaron 400 niños mexicanos que presentaban, al menos, un factor de riesgo neonatal de hipoacusia. La media de la edad de los niños estudiados fue 6,6 meses y la media de la edad gestacional al nacer, 35,1 semanas. El 51% de ellos fueron tratados con amikacina. Se registraron 1 427 factores de riesgo (3,5 por niño), entre los que predominaron la exposición a ototóxicos, la hiperbilirrubinemia y el peso al nacer <1 500 g. En 27% se encontraron alteraciones auditivas de tipo periférico y en 13%, ausencia de respuesta a estímulos auditivos. El bajo peso y la menor edad gestacional al nacer, la concentración máxima de bilirrubina en el suero, la presencia de sepsis, la hemorragia subependimaria o intraventricular, la ventilación mecánica y la exposición a ototóxicos se asociaron significativamente con la presencia de hipoacusia grave o profunda.