

## Research Article

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# Determination of Neonatal Hearing Loss Related to the Use of Amikacin in Patients with Neonatal Sepsis through Screening with Otoacoustic Emissions in the General Hospital of San Jose Iturbide, Guanajuato, Mexico

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## Abstract

Hearing loss is an important problem during childhood, since the intellectual and social development of the child is closely linked to auditory afferences to the central nervous system. The disabling potential of hearing loss depends to a large extent on the precocity with which the diagnosis is made and the time when treatment and rehabilitation is initiated. The evaluation to identify hearing loss in neonates using otoacoustic emissions as a screening method has a sensitivity of 91% and a specificity of 85%, being ideal in this population group. Here we report a descriptive study on neonatal hypoacusia related to treatment with Amikacin done in the Neonatology Unit of the Department of Pediatrics of the General Hospital, San José Iturbide, Gto during the period comprised from January 2016 to October 2018. Fifty five patients were included who had undergone neonatal sepsis and received Amikacin at a dose of 12 mg / kg / day for a variable number of days (7 to 21) according to medical indication. Auditory screening with Otoacoustic Emissions was performed, observing that in 48/55 cases the test was approved (“approved”), and 7/55 cases did not approve the test (“failed”). In the "failed" group, a second evaluation was made with Otoacoustic Emissions, 3 months later. 7/55 patients were reassessed, finding that 6/55 patients now approved the test while only 1/55 cases failed the test. Therefore, the incidence of neonatal hearing loss associated with Amikacin therapy in patients with neonatal sepsis was of 1/55 cases.

**Keywords:** Neonatal sepsis; Otoacoustic emissions; Amikacin; Hearing loss

## 1. Introduction

The World Health Organization (WHO) estimates that around 10% of the world population have some type of disability [1]. The World Bank has noted that more than 400 million people live with disabilities in developing countries and that out of them, 85 million live in Latin American countries [2]. Hearing loss is the most frequent sensory deficiency in humans. Hearing loss is considered as a disability by the WHO when the auditory thresholds of the best hearing ear is greater than 30 dB in frequencies ranging from 0.5 to 4 KHz, in individuals from 0 to 14 years of age; and when these thresholds are greater than 40 dB in individuals 15 years of age or older. Based on 42 population studies, the WHO estimated that 5.3% of the world population had a hearing disability in 2012. However, the prevalence of this type of hearing loss varies in different regions of the world, being predominant in Southern Asia, sub-Saharan Africa and the Asia-Pacific region. Out of the 360 million people in the world who live with a hearing disability, 32 million (9%) belong to the 0 to 14 years of age group. The greatest number of individuals affected by hearing loss pertaining to the group of less than 15 years of age, lives in Southern Asia [3]. In this age group, the prevalence decreases exponentially according to the annual per capita product in the region and decreases linearly according to the higher prevalence of literacy among parents [3].

Efforts have been made to determine the number of people with disabilities and their characteristics in Mexico. The results obtained come from census ballots, from the National Survey of Invalids made by the Ministry of Health (in 1982), from the census, Population and Housing from 1995, from the National Registry of Minors with Disabilities carried out in 1995 by the National Institute of Statistics, Geography and Informatics, from the National System for the Integral Development of the Family, from the Public Education Ministry and from the XII General Census Population and Housing 2000. Based on the recommendations made by the United Nations Organization (UN, 1997), on the International Classification of Deficiencies and Disabilities, on the International Classification of Diseases ICD-10 and on the Survey on Disabilities, Deficiencies and Health Status, of the National Institute of Statistics of Spain (1999), a Mexican classification was elaborated for the hearing disabilities that uses the National Institute of Statistics and Geography of Mexico data [4].

This classification includes descriptions that relate to total hearing loss in one or both ears, or partial, but intense loss, or severe loss, in one or both ears. Descriptions referring to the use of an auditory device are also classified in this last subgroup, although they do not indicate the degree of hearing deficiency in the subjects. This subgroup includes mute-deaf people since, in many cases muteness is a consequence of hearing loss. Vague or ambiguous descriptions such as “does not hear well”, “does not listen well” or “hears a little”, are excluded since the degree of the limitation cannot be determined.

The results of the XII General Census of Population and Housing, 2000 [4], together with the criteria described above, showed that in 2000 about 281 thousand people had hearing disabilities and that in 16.2% of the cases the

origin occurred around birth. The highest prevalence of hearing impairment was observed in Yucatán, with 4.4 cases per thousand inhabitants, followed by Zacatecas and Hidalgo, both with 4.0 cases per thousand inhabitants. The entities with lower prevalence were Baja California (1.7), Chiapas (1.9) and Quintana Roo (2). In 2000 [4], 34.8% of people with hearing disabilities were illiterate. Illiterate subjects are persons without the ability to read and write and who are 15 years of age or older. Only 5.9% of the people with hearing impairment in this age group had completed basic education, 4.4% had ended middle education and 3.2% had attained higher or postgraduate studies. Results also showed that 31.2% of people with hearing disabilities resided in rural areas and only 41.4% had access to health services, of which 80.6% were affiliated to the Mexican Institute of Social Security. However, in rural areas only 19.2% of people with this type of disability had Social Security.

Studies on the prevalence of hearing loss in Mexico are scarce. In a systematic review on prevalence of neurodevelopmental disorders in Mexico [5], frequency of hearing loss was assessed, but there were methodological deficiencies that prevent generalization of the results. However, the findings from two studies are worth mentioning: one was carried out in a low-risk population and another in a population at high risk of hearing impairment. In the first study, a prevalence of 0.65 per 1,000 newborns was observed when studying 3066 children that were treated in a private hospital in the city of Monterrey, Nuevo Leon. Patients were identified by universal screening at two stages [6]. In the second study, a frequency of 2.6% was estimated in a work done in 6,000 children who required care at birth in an ICU at a high specialty public hospital in Mexico City. There was a 15 year follow-up of the patients in this study in whom behavioral and behavioral audiological studies and electrophysiological studies [7] were performed.

The prevalence of hearing loss due to hereditary causes in Mexico could be similar to that which has been found in other countries. Few studies have been done on the general prevalence of the different genetic mutations. In an analysis performed in 11 patients from Mexico City, there was a homozygous patient for c.35delG; a heterozygote patient for c.35insG, a heterozygous patient for c.34G> T and two heterozygous patients for the c.79G>. Authors did not identify the polymorphism (p.V27I), in addition to mutations c.167delT and c 235delC [8]. Studies conducted in Mexico regarding the presence of cytomegalovirus infection and hearing loss are also scarce. In the city of San Luis Potosí, a frequency of 0.89% of congenital cytomegalovirus infection was estimated in 560 live births in a public general hospital. Most patients came from rural areas [9].

The main risk factors to develop hearing loss were evaluated in a comparative study done in 146 children with sensorineural hearing loss and in 272 children with normal hearing capacity from the neonatal ICU in a high specialty public hospital in Mexico City. These risk factors were: low birth weight, prolonged stay in the Intensive Care Unit, the use of mechanical ventilation, high bilirubin concentrations, the prevalence of transfusion, ventricular hemorrhage and the diagnosis of meningitis. Here we studied neonatal secondary hearing loss related to the use of amikacin in patients that had undergone neonatal sepsis. The study was conducted in the Neonatology Unit of the Pediatrics Department of the General Hospital, San Jose Iturbide in Guanajuato, during the period from January 2016 to October 2018. The diagnostic method used was the otoacoustic emissions (OAE) measurement, since this

evaluation has been used as a screening method with a sensitivity of 91% and a specificity of 85%. The study might contribute to establish preventive and rehabilitation measures that lessen the negative effect on future disorders of language and cognitive abilities in these patients.

## **2. Methods**

This was a descriptive study, in which hypoacusis related to the use of Amikacin in neonates meeting the clinical criteria of neonatal sepsis by OAE was determined. The study was done in the Department of Pediatrics of the Hospital General San José Iturbide Gto, during the period of January 2016 to October 2018. All neonates admitted to the Neonatology service with a clinical diagnosis of neonatal sepsis and treated with intravenous Amikacin for 7 days or more at a dose of 12 mg / kg / day were included. Fifty-five neonates were included.

### **2.1 Inclusion criteria**

- a) Neonates with a clinical diagnosis of neonatal sepsis
- b) Patients that received treatment with intravenous Amikacin for 7 days or more at a dose of 12 mg / kg / day
- c) Children with no congenital malformations.

### **2.2 All patients who had the following criteria were excluded**

- a) Children having a history of Leucomalacia
- b) Neonates having a family history of deafness
- c) Children having congenital infections by the TORCH group
- d) Neonates with upper respiratory diseases at the time of evaluation by otoacoustic emissions
- e) Neonates with neonatal sepsis treated with intravenous Amikacin for less than 7 days at a dose of 12 mg / kg / day.
- f) Male or female neonates under 30 weeks of gestational age.

Subsequently, an OAE test was performed. The speech pathologist in charge of neonatal auditory screening was responsible for the examination. OAE were measured during physiological sleep, four weeks after treatment with Amikacin. A small microphone (olive) contained in a probe was introduced into the right and left external auditory canal of the child. The sound generated by this device is only perceived by the patient as a vibration. The resulting emission is captured by a microphone, analyzed, digitized and processed by the specially designed OAE hardware and software. The results of the examination were recorded. The results of the test were classified as “approved” or “failed” for each ear. An electronic database was made in Windows Excel for later statistical analysis in the SPSS statistical package. The Chi-square test was employed since variables were categorical.

## **3. Results**

The study included 55 patients, 17 female and 38 male neonates, who met the inclusion criteria. They had undergone neonatal sepsis and received treatment with amikacin at the dose and for the duration in days established as criteria

of inclusion. Of the patients who received treatment with amikacin, 27 cases received the drug 7 days, 23 cases received it for 10 days, 3 cases for 14 days and 2 cases during more than 15 days (Table 1).

| <b>Amikacin Use 12mg/kg/day (IV)</b> | <b>Number of patients</b> | <b>Percentage</b> | <b>P Value</b> |
|--------------------------------------|---------------------------|-------------------|----------------|
| Less than 7 days                     | 27                        | 49.09%            | >0.005         |
| 8 to 10 days                         | 23                        | 41.81%            | >0.005         |
| 11 to 14 days                        | 3                         | 5.45%             | >0.005         |
| 15 to 21 days                        | 2                         | 3.63%             | >0.005         |
| Total                                | 55                        | 100%              |                |

**Table 1:** Classification by days of duration of treatment with Amikacin in patients with neonatal sepsis who underwent screening with OAE.

Auditory screening with OAE was performed on these patients, observing that in 48/55 cases, patients approved the test (“Approved”), and in 7/55 cases the test was failed (“failed”). (Table 2) Out of the patients that failed the test, 1 was female and 6 were male.

| <b>OAE Results</b> | <b>Female</b> | <b>Male</b> | <b>Total</b> | <b>Percentage</b> | <b>p Value</b> |
|--------------------|---------------|-------------|--------------|-------------------|----------------|
| Approved           | 16            | 32          | 48           | 87.27%            | 0.308          |
| Failed             | 1             | 6           | 7            | 12.72%            | 0.308          |
| Total              | 17            | 38          | 55           | 100%              | -              |

**Table 2:** Determination of hearing loss related to the use of Amikacin in neonates with neonatal sepsis by screening with OAE.

Patients that failed the test were sent to a second evaluation by OAE, during the 3 subsequent months. A total of 7/55 patients were re-evaluated obtaining the result of 6/55 patients who approved the test this time and only 1/55 cases failed the test. The case that failed the test was sent to a specialist for the performance of an evoked potentials test and for the corresponding management. Thus, the incidence of neonatal hearing loss associated with the treatment with amikacin obtained in our series of patients with neonatal sepsis was of 1/55 cases (18.18/1000). (Table 3).

| <b>OAE Results</b> | <b>Female</b> | <b>Male</b> | <b>Total</b> | <b>Percentage</b> | <b>P Value</b> |
|--------------------|---------------|-------------|--------------|-------------------|----------------|
| Approved           | 0             | 6           | 6            | 85.71%            | 0.131          |
| Failed             | 1             | 0           | 1            | 14.28%            | 0.131          |
| Total              | 1             | 6           | 7            | 100%              | -              |

**Table 3:** Evaluation of OAE in patients with unsuccessful testing (“Fail”) for the determination of hearing loss related to the use of Amikacin in a patient with neonatal sepsis.

The associated risk factors for hearing loss in patients with neonatal sepsis treated with amikacin documented were: Prematurity in 40/55 cases, low weight at birth in 40/55, preterm labor 13/55 cases Chorioamnionitis (2/55 cases) Table 4.

| <b>Associated Factors</b> | <b>Number of patients</b> | <b>Percentage</b> | <b>P Value</b> |
|---------------------------|---------------------------|-------------------|----------------|
| Prematurity               | 40                        | 72.72%            | 0.048          |
| Low weight at birth       | 40                        | -                 | 0.048          |
| Labor before term         | 13                        | 23.63%            | 0.001          |
| Chorioamnionitis          | 2                         | 3.63%             | <0.005         |

**Table 4:** Classification of Associated Factors in patients who were diagnosed with hearing loss related to the use of Amikacin in neonates with neonatal sepsis by screening with OAE.

In the classification by gestational age, 15/55 patients had gestational age greater than 37 weeks, 30/55 patients fell within the range of 35 to 36 weeks of gestation, 10/55 cases had 33 and 34 gestational weeks. Therefore gestational age was an associated risk factor. Prematurity is a risk factor for the development of neonatal sepsis (observed in 30/55 patients). Regarding the classification by weight at birth, 31/55 cases showed a weight at birth of less than 2000 grams.

#### **4. Discussion**

We included 55 patients for the study who met the inclusion criteria. They had undergone documented neonatal sepsis and received therapeutics with amikacin at a dose of 12 mg / kg / day for a variable duration in days (ranging from 7 to 21 days) according to medical indication. Auditory screening with OAE was performed on these patients, observing that in 48/55 of cases, they approved the test, and in 7/55 cases the test was failed. In the group of patients that failed the test, a second evaluation was made with OAE, 3 months later. A total of 7/55 patients were reassessed obtaining the result of 6/55 patients who approved the test and 1/55 cases that failed the test. Therefore, the incidence of neonatal hearing loss associated with the therapy with amikacin in patients with neonatal sepsis was of 1/55 cases (18.18/1000). 6/55 cases had a transient hearing loss secondary to the therapy with amikacin, because during the second evaluation of OAE the test was satisfactorily surpassed. Therefore, we document an incidence of 1/55 cases (1.4%) of neonatal hearing loss secondary to the therapy with amikacin in patients with neonatal sepsis. The confirmed patient with hearing loss was referred to a specialist for diagnostic confirmation studies and to provide him with the appropriate therapy. Prolonged use of aminoglycosides (amikacin) represent a risk of otoacoustic damage, and regulation of the time of exposure to the medication should be implemented.

#### **5. Conclusions**

A better knowledge of the ototoxicity induced by drugs will allow for a better care of patients and for the implementation of precautions when administering drugs with ototoxic potential which may have serious consequences in the quality of life of patients. Language is the foundation for cognitive skill acquisition in children.

Therefore, the effects of hearing loss can affect learning, the ability to understand and regulate emotions and the capacity to perform complex motor tasks. As a consequence, a universal neonatal audiological evaluation is recommended for all newborns. Hearing loss should be assessed during the first month after birth and presence of hearing loss should be definitively diagnosed at 3 months of age for appropriate interventions to be instituted at 6 months. Tests that should be implemented include the evoked OAE test, the brainstem auditory response test or a combination of both. These tests should mainly be done in patients suffering from risk pathologies (meningitis, sepsis, among others) and in patients subjected to therapeutic risks (aminoglycosides, among others). The dose-dependent side effects at the hearing level and the duration of treatment as well as the underlying pathology should be taken into account in addition to associated risk factors, mainly in patients entering neonatal intensive care areas. Considering the findings of neonatal hearing loss related to the therapy with amikacin in patients with neonatal sepsis documented by OAE, we recommend the restoration of areas where these tests can be performed in the Growth and Development Units clinics, such as in the Clínica de Niño Sano of the Roosevelt Hospital.

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