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# Auditory assessment of neonates at high risk of hearing impairment admitted to the intensive care unit

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***Abstract*---**Background: Permanent hearing loss is a common neonatal health problem which leads to deleterious effects on language, speech development and academic outcome. Its prevalence is much higher in newborns that need neonatal intensive care admission. Methods: This is a cross-sectional study included 314 neonates admitted to neonatal intensive care unit. The inclusion criteria included neonates with risk factors of hearing loss. They were all evaluated by Transient Evoked Otoacoustic Emissions (TEOAE). Automated auditory brainstem response (AABR) was done at 3 months of age for those who failed TEOAE screening. Results: Out of 314 neonates, 4.5% were diagnosed by permanent hearing loss. No statistical significance was detected between hearing loss and gender (P = 0.61), prematurity (P = 0.529) and birth weight (P = 0.076). The most common risk factor detected was ototoxic drug intake, with aminoglycosides being the most frequent. There was a significant P value between ototoxic medications and hearing loss (P = 0.018). The highest percentage of cases with hearing loss was detected among neonates who received both aminoglycosides and vancomycin. Conclusion: The prevalence of permanent hearing loss among admitted neonates at risk of hearing loss are high. Therefore, their screening is essential for early detection and hence their early management. Use of aminoglycosides and vancomycin is a major risk factor for hearing loss. Duration of ototoxic drug therapy as well as that of oxygen therapy is of significant association with hearing loss.

***Keywords***---AABR, hearing loss, ototoxic medication, TEOAE.

## Introduction

Permanent hearing loss is a common problem at birth, which can significantly affect the language and speech development and later the academic outcome (Pimperton & Kennedy, 2012). That is why screening newborns for the possibility of hearing loss is necessary for early detection and intervention. It is estimated that the prevalence of moderate, severe and profound hearing loss is 1 in 900 to 2500 newborns. On the other hand, this prevalence is much higher in newborns admitted to neonatal intensive care unit (NICU) (16.7 per 1000 newborn) (Vos et al, 2015). Many factors might play a role in placing these NICU babies at an increased risk of hearing loss including: intrauterine infections (ToRCH), prematurity and low birth weight (< 1500 gm), hyperbilirubinemia at a serum level requiring transfusion, ototoxic medication like aminoglycosides, underlying diseases as bacterial meningitis, and hypoxic ischemic encephalopathy (Wake et al, 2016). In neonatal hearing screening programs, it has been recommended that all newborns should be screened before one month of age using either otoacoustic emissions (OAEs) or automated auditory brainstem response (AABR) through a single stage or 2 stage protocol. Those neonates who fail their screening test should undergo audiological assessment by age of 3 months and early intervention for those with definitive hearing impairment by age of 6 months (Patel & Feldman, 2011).

Two techniques are used in hearing screening, otoacoustic emissions (OAE) and automated auditory brainstem response (AABR) (Foust et al, 2013). OAEs are sound waves that are present in the ear canal as a result of the vibration of the outer hair cells of the cochlea and backward transmission of these waves through the middle ear (Akinpelu et al, 2014). OAEs are non-invasive, rapid, and an appropriate method for assessing cochlear function (Khairy et al, 2018). AABR measures the summation of action potentials from the 8th nerve to the inferior colliculus of midbrain (Barbee et al, 2018). Subsequent management of hearing impairment should be done by a multidisciplinary team that is skilled in caring for infants and children with hearing loss that includes audiologists, otolaryngologists, speech pathologists, geneticists, and educational specialists (Alford et al, 2014).

## Patients and methods

This is a cross sectional analytical study, that included 314 neonates who were admitted at neonatal intensive care unit of Cairo University hospitals from 1st of August 2019 till 31st of July 2021. An informed consent was obtained from parents of neonates after explanation of study aim and its benefits.

## Inclusion criteria

Neonates with high risk for hearing loss as defined by the Joint Committee on Infant Hearing, 2019 (JCIH, 2019):

1. Family history of hereditary childhood hearing loss
2. Intrauterine infections (ToRCH)
3. Craniofacial anomalies
4. Birth weight < 1500 gm
5. Hyperbilirubinemia at a serum level requiring echange transfusion
6. Ototoxic medication intake (as aminoglycosides and loop diuretics)
7. Bacterial meningitis
8. Apgar score < 4 at 1 minute or < 6 at 5th minute
9. Mechanical ventilation for more than 5 days
10. Stigmata or other findings associated with a syndrome known to include hearing loss

**Exclusion criteria**

1. Conditions interfering with Otoacoustic emissions e. ear discharge
2. Neonates whose parents did not consent for participation in the study

**Methodology**

Detailed data of each neonate will be documented as follows:

- Full detailed history taking: Gestational age, mode of delivery, Apgar score, intrauterine infections, maternal illness or medications, family history of hearing loss.
- Extensive clinical examination: Weight, length, head circumference, craniofacial anomalies.
- Lab investigations: Complete blood picture, C-reactive protein, Cerebrospinal fluid analysis and culture, total and direct serum bilirubin, cranial ultrasonography
- Procedures and medications: during admission and duration of therapy of ototoxic medication
- Full otoscopic examination to exclude presence of ear discharge or external canal stenosis
- Hearing screening by Transient evoked otoacoustic emissions (TEOAE) and Automated Auditory Brainstem response (AABR)

**Procedure**

A handheld screener (Interacoustics SERA device) is used.

1. First stage, TEOAE screening is done before age of 1 month giving a pass or refer response.
2. Second stage, screening after 3-4 weeks of a fail response in the first stage.
3. Third stage, AABR screening immediately after a fail response in the second stage.
4. A fail response in AABR is referred to the Audiology unit for full diagnostic auditory brainstem response at age of 3 months.

**Equipment**

Interacoustics Handheld Sera™ device
Procedure for TEOAE:

- A probe is placed into the external ear canal and sealed snugly using a removable, soft, rubber ear tip.
- Start button is pressed for each ear separately.
- A pass or refer response is documented

The following default analytical parameters were used for interpreting the response automatically:

- Probe stability > 70%
- Stimulus intensity: 79 to 83 dB SPL
- Signal reproducibility >70%
- Response amplitude ≥ 6 dB SPL over noise spectrum in three consecutive frequencies.
- Interpreted bands: 1, 1.5, 2, 3, 4 Hz
- Analysis window: 12 ms

Procedure for AABR:

1. Skin cleaning with an abrasive substance at forehead and behind both ears
2. Positive (active) electrode is placed on forehead and 2 negative (reference) electrodes behind both ears at mastoid process

The following default analytical parameters were used for interpreting the response automatically:

- Stimulus intensity: 80 dB SPL through binaural insert earphones
- Stimulus type: 100 μs rarefaction filtered clicks from 100-3000 Hz
- Stimulus rate: 20.1 clicks per second
- Number of stimuli: 1024
- Analysis window: 15 ms

Both TEOAE and AABR will be conducted during natural sleep with no sedation. Neonate is kept quite as much as possible in a quite separate room.

**Sample size**

Sample size calculation was performed using OpenEpi Version 3.01. The calculated sample size is 182 neonates (if a dropout rate of 10% is added, the sample size would be 200 neonates). This number would detect a 13.7% prevalence of hearing loss in neonates admitted to neonatal intensive care unit at 95% level of confidence and 80% power of study. However, to achieve 99% confidence level, 314 neonates are needed. So, the final sample size is 314 neonates.

**Statistical methods**

Data were statistically described in terms of mean ± Standard Deviation (SD), median, range or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing 2 groups of normally distributed data and Mann Whitney U test for independent samples for comparing not-normal data. Comparison of normally distributed numerical variables between more than two groups was done using one-way analysis of variance (ANOVA) test. Non-normal numerical variables between more than two groups were compared using Kruskal Wallis test. For comparing categorical data, Chi-square ($x^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided p values less than 0.005 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

**Results**

This study was conducted in the NICU of Cairo University children hospitals (Abo El Reesh & Kasr Al-Aini) from 1st of August 2019 till 31st of July 2021. It included 314 neonates with risk factors for hearing impairment as defined by the Joint Committee on Infant Hearing, 2019. The gestational age of the included neonates ranged from 27 to 42 weeks with a median of 36 weeks. The births weights ranged from 1 Kg to 4.45 Kg with a median of 2.313 Kg (Table 1). Among the studies population, only 137 were full term (43.6%). The remaining 177 neonates were preterm, with 88 (28%) being less than 33 gestational weeks and 89 (28.3%) from 33 to 36 gestational weeks ± 7 days old (Fig. 1). In our study, males represented 56% of the total, while females were 44% (Fig. 2). As regards mode of delivery, neonates delivered by caesarian section were 83.8%, while 16.2% were delivered normally by vaginal route (Fig. 3).

Table (1): Demographic data of studied neonates

| | Mean | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| GA (weeks) | 35.1 | 3.01 | 36 | 27 | 42 |
| BW (kg) | 2.324 | 797 | 2.313 | 1.000 | 4.450 |
| Age at 1st OAES-Exam (D) | 17.6 | 7.59 | 18 | 5 | 40 |
| Age at 2nd OAES-Exam (D) | 45.4 | 7.68 | 46 | 30 | 60 |

*D: days; Kg: kilogram; OAES: Oto Acoustic Emission; SD: Standard Deviation*

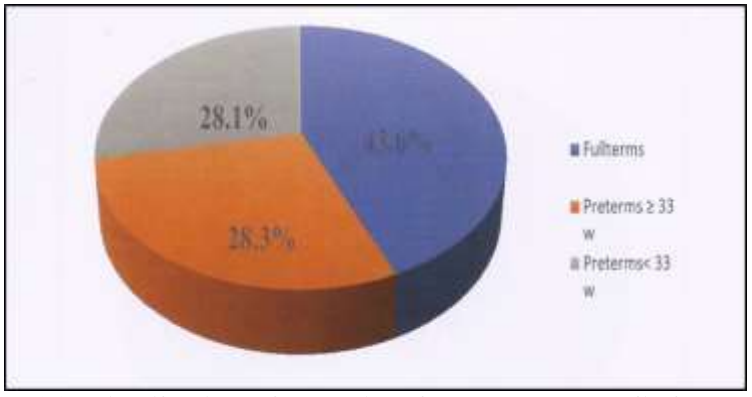


Figure (1): Distribution of gestational age among studied neonates

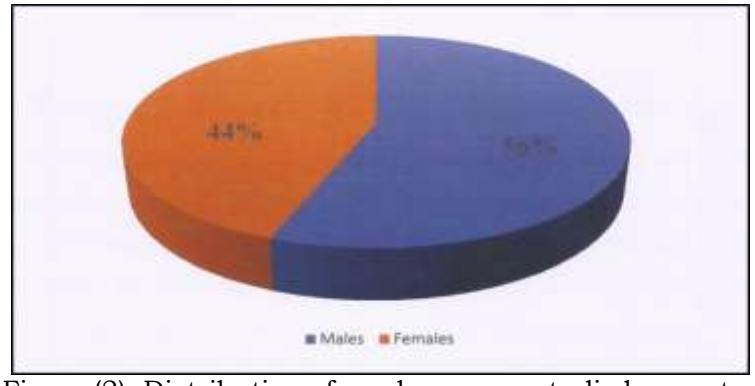


Figure (2): Distribution of gender among studied neonates

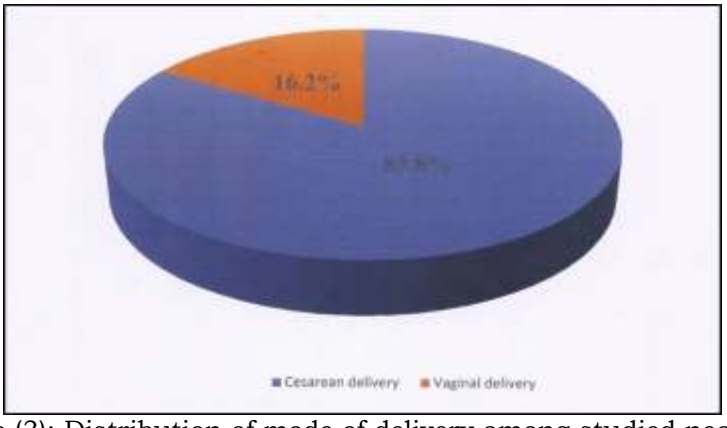


Figure (3): Distribution of mode of delivery among studied neonates

Distribution of Definitive diagnosis among the study population:
Our cases with hyperbilirubinemia were 22%, combined respiratory distress syndrome (RDS) with sepsis were 19.8%, cases with RDS only were 12.4%, combined RDS with necrotizing enterocolitis (NEC) were 11.8%, cases with sepsis only were 9.2%, 7 % had pneumonia, 5.4% had combined sepsis with hyperbilirubinemia, 3.8% had pneumonia with cardiac problems, 2.5% had other diseases (e.g: inborn errors, hemorrhagic diseases), 1.9% had combined sepsis

with cardiac problems, 1.6 % had broncho-pulmonary dysplasia (BPD) in addition to NEC, 1.3% had meningitis and finally 1.3 % had combined sepsis with hypoxic ischemic encephalopathy (HIE) **(**Fig. 4).

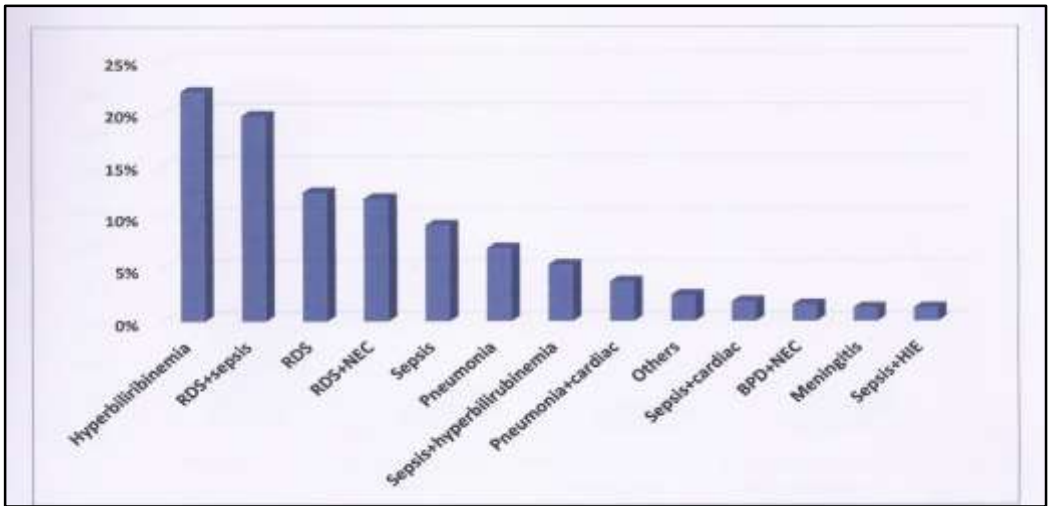


Figure (4): Distribution of definitive diagnosis among studied neonates

Distribution of Hearing outcomes among the study population:
Cases were classified into 4 groups according to hearing screening results:
Group 1: Normal Hearing (Pass in 1st OAE screen) (86.3%)
Group 2: Temporary Hearing loss (Pass in 2nd OAE screen) (6.7%)
Group 3: Mild Hearing loss (Pass AABR only) (3.5%)
Group 4: Permanent Hearing loss (Documented hearing loss in diagnostic ABR at age of 3 months) (4.5%) (Fig. 5).

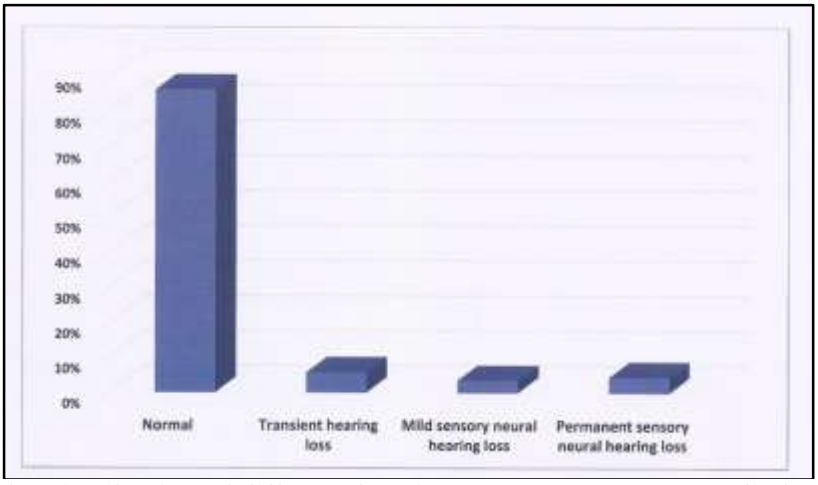


Figure (5): Distribution of different hearing outcomes among studied neonates

The risk factors of hearing loss among the study population:
The most frequent risk factors were ototoxic drugs alone or in combination with prematurity (each accounting for 29% of cases), hyperbilirubinemia (22.9%),

mechanical ventilation > 5 days combined with ototoxic drugs and prematurity (10.2%), hyperbilirubinemia combined with ototoxic drugs (6.1 %), hypoxia combined with prematurity and ototoxic medication (1.6 %), and finally meningitis combined with prematurity and ototoxic drugs (1.3%). Regarding ototoxic drugs, 33.2% received aminoglycosides, 31.6% received vancomycin, 29.9% received both aminoglycosides and vancomycin, 3.7% received both aminoglycosides and frusemide, 1.6% received vancomycin and frusemide (Table 2). Regarding meningitis, 3 CSF cultures were positive for multidrug resistant Klebsiella (Klebsiella MDR) however, all 3 passed the hearing screening. Only one culture was positive for Methicillin resistant staphylococcus aureus (MRSA) and this case developed permanent hearing loss.

Table (2): Distribution of risk factors and ototoxic drugs of studied neonates

| | Number of cases | Percent |
|---|---|---|
| **Risk factors:** | | |
| **Ototoxic drugs** | 91 | 29.0% |
| **Prematurity + ototoxic drugs** | 91 | 29.0% |
| **Hyperbilirubinemia** | 72 | 22.9% |
| **Prematurity + ototoxic drugs + MV>5d** | 32 | 10.2% |
| **Ototoxic drugs + hyperbilirubinemia** | 19 | 6 % |
| **Prematurity + ototoxic drugs + hypoxia** | 5 | 1.6% |
| **Prematurity + ototoxic drugs + meningitis** | 4 | 1.3% |
| **Total** | 314 | 100.0% |
| **Ototoxic drugs:** | | |
| **Aminoglycosides** | 81 | 33.2% |
| **Vancomycin** | 77 | 31.6% |
| **Aminoglycosides + vancomycin** | 73 | 29.9% |
| **Aminoglycosides + frusemide** | 9 | 3.7% |
| **Vancomycin + frusemide** | 4 | 1.6% |
| **Total** | 244 | 100.0% |

Comparative data of the 4 groups of hearing screening:
The mean gestational age of 4 groups ranged from 33.3 to 35.3 weeks with a statistically non-significant difference. The birth weight of neonates ranged from 1 to 4.4 Kg with no statistically significant difference between 4 groups. However, the age at 1st and 2nd OAE screen showed a highly significant statistical difference between the 4 groups of hearing loss (Table 3).

Table (3): Comparison between hearing loss groups

| | G1 (n = 271) | | | | | G2 (n = 18) | | | | | G3 (n = 11) | | | | | G4 (n = 14) | | | | | p value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | |
| GA | 35.1 | 3.0 | 36 | 27 | 42 | 35.3 | 2.9 | 35 | 32 | 40 | 33.3 | 2.7 | 32 | 31 | 38 | 34.7 | 2.7 | 34 | 31 | 38 | 0.226 |
| BW | 2359 | 792 | 2460 | 1000 | 4450 | 2299 | 825 | 2190 | 1180 | 3900 | 1770 | 706 | 1450 | 1200 | 2950 | 2113 | 790 | 1950 | 1100 | 3500 | 0.076 |
| Age at 1st OAES-Exam | 17.0 | 7.6 | 16 | 5 | 40 | 17.3 | 5.1 | 16.5 | 10 | 29 | 24.9 | 4.0 | 25 | 15 | 29 | 22.1 | 7.3 | 24.5 | 5 | 29 | 0.001 |
| Age at 2nd OAES-Exam | 45.0 | 7.6 | 44 | 30 | 60 | 44.6 | 6.8 | 45 | 30 | 58 | 52.4 | 4.3 | 54 | 44 | 58 | 49.3 | 8.9 | 51.5 | 33 | 60 | 0.003 |

*GA: gestational age, BW: Birth weight, OAEs: Oto acoustic emissions*
*G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss*

Gestational age, gender and mode of delivery description between 4 groups:
There was no statistical difference between 4 groups as regard prematurity, gender, mode of delivery (Table 4).

Table (4): Gestational age, gender, & mode of delivery of 4 groups

| | G1 (n = 271) | | G2 (n = 18) | | G3 (n = 11) | | G4 (n = 14) | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | |
| **Age description:** | | | | | | | | | |
| FT | 122 | 45.0% | 8 | 44.4% | 2 | 18.2% | 5 | 35.7% | 0.529 |
| PT ≥ 33 w | 76 | 28.0% | 5 | 27.8% | 3 | 27.3% | 5 | 35.7% | |
| PT< 33 w | 73 | 26.9% | 5 | 27.8% | 6 | 54.5% | 4 | 28.6% | |
| Total | 271 | 100.0% | 18 | 100.0% | 11 | 100.0% | 14 | 100.0% | |
| **Gender** | | | | | | | | | |
| Males | 155 | 57.2% | 8 | 44.4% | 5 | 45.5% | 7 | 50.0% | 0.610 |
| Females | 116 | 42.8% | 10 | 55.6% | 6 | 54.5% | 7 | 50.0% | |
| Total | 271 | 100.0% | 18 | 100.0% | 11 | 100.0% | 14 | 100.0% | |
| **Mode of delivery:** | | | | | | | | | |
| CS | 224 | 82.7% | 15 | 83.3% | 10 | 90.9% | 14 | 100.0% | 0.338 |
| VD | 47 | 17.3% | 3 | 16.7% | 1 | 9.1% | 0 | 0.0% | |
| Total | 271 | 100.0% | 18 | 100.0% | 11 | 100.0% | 14 | 100.0% | |

*FT: full term PT: preterm CS: caesarian delivery VD: Vaginal delivery, w: weeks*
*G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss*

Description of definitive diagnosis between groups:
As regard cases with both RDS and sepsis, they had a higher affection by mild and permanent hearing loss (Table 5).

Table (5): Comparison between 4 groups regarding diagnosis

| | G1 (n = 271) | | G2 (n = 18) | | G3 (n = 11) | | G4 (n = 14) | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | |
| **Hyperbilirubinemia** | 65 | 24.0% | 2 | 11.1% | 0 | 0.0% | 2 | 14.3% | 0.001[a,b] |
| **RDS + Sepsis** | 54 | 19.9% | 1 | 5.6% | 4 | 36.4% | 3 | 21.4% | |
| **RDS** | 34 | 12.5% | 4 | 22.2% | 0 | 0.0% | 1 | 7.1% | |
| **RDS + NEC** | 29 | 10.7% | 5 | 27.8% | 2 | 18.2% | 1 | 7.1% | |
| **Sepsis** | 26 | 9.6% | 2 | 11.1% | 0 | 0.0% | 1 | 7.1% | |
| **Pneumonia** | 20 | 7.4% | 1 | 5.6% | 0 | 0.0% | 1 | 7.1% | |
| **Sepsis + hyperbilirubinemia** | 14 | 5.2% | 0 | 0.0% | 1 | 9.1% | 2 | 14.3% | |
| **Pneumonia + Cardiac** | 9 | 3.3% | 2 | 11.1% | 0 | 0.0% | 1 | 7.1% | |
| **Others** | 7 | 2.6% | 1 | 5.6% | 0 | 0.0% | 0 | 0.0% | |
| **Sepsis + Cardiac** | 4 | 1.5% | 0 | 0.0% | 2 | 18.2% | 0 | 0.0% | |
| **BPD + NEC** | 3 | 1.1% | 0 | 0.0% | 2 | 18.2% | 0 | 0.0% | |
| **Meningitis** | 3 | 1.1% | 0 | 0.0% | 0 | 0.0% | 1 | 7.1% | |
| **Sepsis + HIE** | 3 | 1.1% | 0 | 0.0% | 0 | 0.0% | 1 | 7.1% | |
| **Total** | 271 | 100.0% | 18 | 100.0% | 11 | 100.0% | 14 | 100.0% | |

*RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis,*
*BPD: bronchopulmonary dysplasia, HIE: hypoxic ischemic encephalopathy*
*G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss; a: significant difference between group 1 and group 3; b: significant difference between group 2 and group 3*

The risk factors among the 4 groups:

Regarding comparison of risk factors between 4 groups, ototoxic drugs alone and in combination with prematurity showed a higher percentage of mild and permanent hearing loss than the other risk factors (Table 6).

Table (6): Comparison between 4 groups regarding risk factors

| | 1 (n = 271) | | 2 (n = 18) | | 3 (n = 11) | | 4 (n = 14) | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | |
| **Ototoxic drugs** | 77 | 28.4% | 8 | 44.4% | 3 | 27.3% | 3 | 21.4% | 0.086 |
| **Prematurity + ototoxic drugs** | 80 | 29.5% | 5 | 27.8% | 3 | 27.3% | 3 | 21.4% | |
| **Hyperbilirubinemia** | 69 | 25.5% | 1 | 5.6% | 0 | 0.0% | 2 | 14.3% | |
| **Prematurity + ototoxic drugs + MV>5days** | 23 | 8.5% | 3 | 16.7% | 4 | 36.4% | 2 | 14.3% | |
| **Ototoxic drugs + hyperbilirubinemia** | 15 | 5.5% | 1 | 5.6% | 1 | 9.1% | 2 | 14.3% | |
| **Prematurity + ototoxic drugs + hypoxia** | 4 | 1.5% | 0 | 0.0% | 0 | 0.0% | 1 | 7.1% | |
| **Prematurity + ototoxic drugs + meningitis** | 3 | 1.1% | 0 | 0.0% | 0 | 0.0% | 1 | 7.1% | |
| **Total** | 271 | 100.0% | 18 | 100.0% | 11 | 100.0% | 14 | 100.0% | |

*MV: mechanical ventilation G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss*

Distribution of ototoxic drugs among the 4 groups:
In terms of ototoxic drugs, those who received aminoglycosides alone had a higher rate of temporary hearing loss than other drugs. However, those who received combined aminoglycosides and vancomycin had the highest rate of permanent hearing loss (Table 7).

Table (7): Comparison between 4 groups regarding ototoxic drugs

| | G1 (n = 271) | | G2 (n = 18) | | G3 (n = 11) | | G4 (n = 14) | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | |
| **Aminoglycoside** | 72 | 35.3% | 8 | 47.1% | 0 | 0.0% | 1 | 8.3% | 0.018 [a,b] |
| **Vancomycin** | 63 | 30.9% | 7 | 41.2% | 5 | 45.5% | 2 | 16.7% | |
| **Aminoglycoside + Vancomycin** | 59 | 28.9% | 1 | 5.9% | 5 | 45.5% | 8 | 66.7% | |
| **Aminoglycosides + Frusemide** | 7 | 3.4% | 1 | 5.9% | 0 | 0.0% | 1 | 8.3% | |
| **Vancomycin + Frusemide** | 3 | 1.5% | 0 | 0.0% | 1 | 9.1% | 0 | 0.0% | |
| **Total** | 204 | 100.0% | 17 | 100.0% | 11 | 100.0% | 12 | 100.0% | |

*G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss; a: significant difference between group 2 and group 3; b: significant difference between group 2 and group 4*

The cumulative duration of oxygen exposure and ototoxic drugs among the 4 groups: The mean of oxygen exposure was 6, 7.8, 12.6, 9.1 days respectively with a significant P value. Also, the mean of total duration of ototoxic drugs intake of the 4 groups were 10.7, 10.8, 17, and 15.4 respectively with a significant P value (Table 8).

Table (8): Comparison between 4 groups regarding cumulative oxygen and ototoxic drug duration

| | G1 (n = 271) | | | | | G2 (n = 18) | | | | | G3 (n = 11) | | | | | G4 (n = 14) | | | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | Mean | SD | Median | Min | Max | value |
| Cumulative O2 duration | 6.0 | 6.5 | 5 | 0 | 27 | 7.8 | 5.6 | 7 | 0 | 19 | 12.6 | 10.2 | 8 | 0 | 28 | 9.1 | 5.6 | 10 | 0 | 15 | 0.003[a] |
| Ototoxic drugs Duration | 10.7 | 7.9 | 10 | 0 | 36 | 10.8 | 4.7 | 10 | 0 | 20 | 17.0 | 4.1 | 14 | 14 | 25 | 15.4 | 8.2 | 19.5 | 0 | 25 | 0.010[a] |

*G1: normal; G2: transient hearing loss; G3: mild sensory neural hearing loss; G4: permanent sensory neural hearing loss; a: significant difference between group 1 and group 3*

Finally, the 14 neonates who developed permanent hearing loss were all born with CS delivery, 7 were full term and 9 were preterm. The most common risk factor

amongst them was ototoxic drug intake, with the highest number in those who received combined aminoglycosides and vancomycin. They were referred to audiology department for further management and follow up. The remaining cases were advised to follow up with the audiology department to rule out the possibility of late onset hearing loss.

**Discussion**

Permanent hearing loss is a common problem at birth. The prevalence is much higher in newborns admitted to neonatal intensive care unit (NICU). This cross-sectional study included 314 neonates, who had a risk factor of hearing impairment as defined by the Joint Committee of Infant Hearing (JCIH, 2019). The gender distribution was (55.7%) males and (44.3%) females, reflecting a generally higher rate of male admission to NICU which may be related to the higher vulnerability of male gender to preterm delivery secondary to differences in gene expressions between placentae of male and female fetuses (Challis et al, 2013).

There was a higher prevalence of preterm neonates (56.4%) than full term neonates (43.6%) in this study with mean gestational age being 35 ± 3 weeks. There was also a higher incidence of caesarian section (CS) delivery (83%) compared to vaginal delivery (16.2%) which is in line with Egypt's demographic and health survey (EDHS, 2014) which stated that 87% of all live births are delivered in hospitals and a slightly more than half of births (52%) by CS. This represented a sharp increase from 2008 when only 28% of births were by CS. This could be due to the high incidence of elective CS deliveries in addition to emergency CS of high-risk pregnancies.

In our study, the majority of the cases were diagnosed with Hyperbilirubinemia (22.8%), respiratory distress syndrome (RDS) with neonatal sepsis (19.7%), Necrotizing Enterocolitis (11.8%) followed by pneumonia, cardiac problems, meningitis, and hypoxic ischemic encephalopathy. The cases in this study were categorized into 4 groups according to the results of hearing screening: Group 1 Normal hearing (86.3%) that passed the 1st OAEs screen, Group 2 Temporary hearing loss (6.7%) that had a refer response in 1st OAEs screen but passed the 2nd screen, Group 3 Mild hearing loss (3.5%) that had a refer response in both OAEs screens with normal AABR screen, and Group 4 Permanent hearing loss (4.5%) that failed all screens and had a diagnostic ABR at age of 3 months with definitive hearing loss diagnosis. Those results were similar to (Kumar et al, 2016) which was a descriptive study conducted in level III NICU of JIPMER, a tertiary care hospital in Pondicherry, India. They concluded that 93% of cases were normal, 1% had temporary hearing loss, 1% had mild hearing loss, and 5 % had permanent hearing loss.

In a study by (Molini et al, 2016) the prevalence of hearing loss was 2% among well babies and 4.3% among infants who were at risk of hearing loss. Similar prevalence was reported in the study of (Rai & Thakur, 2013) in which the prevalence of hearing loss in infants admitted to the neonatal intensive care unit (NICU) was 4.9%. Ototoxic medications together with prematurity represented the most common risk factor for hearing impairment in our study. Both risk factors

were present in 29% of cases followed by Hyperbilirubinema (22.9%), mechanical ventilation > 5 days (10.2%), combined ototoxicity with hyperbilirubinemia (6.1%), hypoxia (1.6%), and meningitis (1.3%). These results were similar to (El-sheikh et al, 2020) which was carried out on 58 newborns with risk factors for hearing impairment admitted to NICU of pediatric department, Zagazig University Hospital. They reported that ototoxic medication was the most common risk factor identified in the studied group (82.8 %) followed by assisted ventilation > 5 days (77.6%), prematurity (62.1%), Low birth weight (56.9%), septicemia (50%) and perinatal asphyxia (13.8%).

Also, (Wroblewska-Seniuk et al, 2017) who performed a study on preterm neonates found that the most frequent risk factor in preterm neonates < 33 weeks was exposure to ototoxic medications (63%) followed by low birth weight < 2500 g (53.3%) and treatment in the NICU (43.9%). The use of ototoxic medications was also the most frequent risk factor in neonates > 33 weeks of gestation (1.72%) in another study conducted by (Hardani et al, 2020) in which 530 infants with different risk factors were screened. It found that ototoxic drugs and hyperbilirubinemia requiring exchange transfusion were the commonest risk factors followed by asphyxia, low birth weight weight, Apgar score < 5. Maqbool et al, 2015 also reported that ototoxic medications and hyperbilirubinemia were the major risk factors in studied neonates.

On the other hand, other studies showed different prevalence of risk factors for hearing impairment in NICU. In a study conducted by (Di Stadio et al, 2019) the most prevalent risk factors were prematurity < 28 weeks, neurological disorders, craniofacial malformations, and sepsis. Additional risk factors for hearing loss included maternal disease during pregnancy, Cesarean delivery, and twin pregnancy. The most frequently used ototoxic drugs used in our study were aminoglycosides (33.2%) followed by vancomycin (31.6%), combined aminoglycosides and vancomycin (29.9%), aminoglycosides and frusemide (3.7%), and both vancomycin and frusemide (1.6%).

Our results were in agreement with (Khairy et al, 2018) that reported that mechanical ventilation > 5 days, sepsis, usage of aminoglycosides, loop diuretics, vancomycin alone or in combination with aminoglycodides, and prolonged duration of NICU admission were considered risk factors of hearing impairment. Also, a study by (Hrnčić, 2018) showed that exposure to ototoxic medications was a major risk factor identified in more than half of the newborns at risk of hearing impairment. They reported that half of the newborns treated with ototoxic medication received gentamycin for at least 5 days. The wide use of aminoglycosides can be partially explained by the predominance of gram –ve infections in NICUs. Also, aminoglycosides in association with β-lactams are often considered the first line antibiotics in newborns.

In the present study, there was no statistical significance regarding birth weight as well as prematurity with hearing loss. This is in agreement with (Hardani et al, 2020). However, in contrast to this finding, a study conducted by (Regina et al, 2017) reported that 31.5% and 28.9% of newborns suffering from hearing impairment were born prematurely (gestational age ≤ 36 weeks) and were of low birth weight (< 1500 gm) respectively. Also, (Gouri et al, 2015) reported that low

birth weight was a significant risk factor for hearing impairment. In our study, there was no statistical significance between gender and hearing impairment. This is consistent with previous several studies (Al-Meqbel & Al-Baghli, 2015; Karaca et al, 2014).

There was no significant relation between mode of delivery and hearing impairment in our study. This is in agreement with (Güven, 2019) which reported that in both modes of delivery, most newborns failed the first screen, while a majority successfully completed the second screen. Another retrospective study, conducted by (Xiao et al, 2015), reported significant high rates of failure in the first OAE screen among those born by CS. However, failure rates in OAE screen were seen to decrease in both modes of delivery as time between birth and screening increased. This could be explained by the receding of amniotic fluid remnants from external ear canal which usually affects OAE results. The same results were also reported by (Smolkin et al, 2013), where the group screened beyond 48 hours after delivery had 7.7 fold lower failure rates than the group screened within 48 hours after delivery. Also, the former had a six fold less need for repeating the hearing OAE screen.

In our study, cases that had RDS with sepsis had a higher frequency of mild and permanent hearing impairment compared to the other risk factors. An explanation to this result can be partially demonstrated by (Shim et al, 2018) which concluded that a high level of Interleukin-6 was found in the neonatal serum of RDS cases with sepsis which is significantly involved in the pathogenesis of hearing impairment. Regarding ototoxic medications used in our study, there was a significant relation between ototoxic drug intake and hearing impairment. Cases who received both aminoglycosides and vancomycin represented 45.5% of cases with mild hearing impairment and 66.7% of cases with permanent hearing impairment which was much higher than the ones who received aminoglycosides alone. The highest percentage of cases with temporary hearing impairment (47.1%) was noticed among those who received aminoglycosides alone. This is similar to the study of (Gohari et al, 2020) in which ototoxicity was the most prevalent risk factor with a significant association between hearing loss and antibiotic therapy. Another study by (Abu Moussa & El Huchi, 2015) reported that there was no statistically significant deterioration in OAEs between group 2 (no antibiotics) and group 1 (received gentamycin only). On the other hand, the combination of vancomycin with gentamycin in group 3 resulted in a statistically significant increase in OAEs failure rate.

Reversible ototoxic effects of aminoglycosides have been reported in animal models. Moreover, transient hearing loss in neonates is reported and could be explained by a transient cochlear dysfunction due to inflammation or delayed maturation of the auditory system (Bramhall et al, 2014). Also, the ototoxicity of aminoglycosides depends on treatment duration, serum peak and trough concentrations, concomitant diseases and simultaneous administration of loop diuretics and vancomycin. In the current study, the mean duration of ototoxic drug intake of the 4 groups ranged from 10.7 – 17 days with a significant difference between them. Similar to our study, the cross-sectional study by (Alaee et al, 2015) found a significant association between hearing loss and gentamycin,

amikacin, tobramycin, and vancomycin. As well as a significant correlation was demonstrated between hearing loss and duration of antibiotic intake.

In the current study, there was a statistically significant relationship between cumulative duration of oxygen therapy and hearing loss. This is consistent with (Pourarian et al, 2012) which showed a significant relationship as well. Other studies demonstrated that prolonged oxygen therapy could lead to late onset sensorineural hearing loss as well (van Noort-van der Spek et al, 2017). Finally, 14 out of 314 neonates in this study were diagnosed with permanent hearing loss. They were referred to the audiology department, Cairo University for further diagnostic hearing tests to detect the severity of the hearing loss and were managed accordingly. As regards the rest of the neonates, a follow up hearing test was recommended at age of 24 – 30 months to exclude the possibility of late onset hearing loss.

**Conclusion**

- Hearing loss among newborns at risk admitted in NICU is still of great concern warranting routine hearing screening and follow up.
- Ototoxic medications and oxygen therapy are major contributors to hearing impairment and require close monitoring of their requirement, adjustment and duration of intake.

**Recommendation**

- All neonates admitted in NICU should undergo hearing screening just before discharge, but not earlier than 5 days of admission to avoid false positive hearing loss results.
- Diagnosis of definitive hearing loss should be done before age of 3 months with early management before age of 6 months.
- Follow up and audiological assessment of cases with normal hearing screening who were at high risk of hearing impairment is needed within 24 – 30 months of age for possibility of late onset hearing loss.
- Careful monitoring of ototoxic drugs as regard dose, duration, serum drug level to avoid/minimize their harmful effects.
- Modulation of antibiotic regimens in NICU to control use of ototoxic medication and avoid/limit harmful combinations.
- Adequate control and close monitoring of oxygen therapy in NICU.
- Hyperbilirubinemia is a major cause of Auditory Dys-synchrony spectrum disorder. It needs screening by combination of AABR & OAE to avoid being missed in the normal OAE only screened groups. A previous paper dedicated to this risk factor alone has been already published by the authors.

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