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Comparison of Auditory Brainstem Response in HIV-1 exposed and unexposed newborns and their correlation with the maternal viral load and CD4 cell counts

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Abstract

Objective—The effects of maternal HIV infection and antiretroviral therapy on hearing of HIV-exposed newborns in sub-Saharan Africa have not been investigated. We determined the prevalence of sensorineural hearing loss among HIV-exposed newborns and the association between the hearing threshold and maternal & newborn parameters.

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Contributions of authors

AJ Fasunla was involved in the study concept and design, data collection, hearing screening and threshold level determination, data collection and analysis and interpretation, writing of the manuscript and final draft approval.

BO Ogunbosi was involved in the study design, data collection and analysis, manuscript drafting and final draft approval of the manuscript.

GN Odaibo was involved in the study design, performed the laboratory test (CD4 counts, viral load and HIV test), data collection, manuscript review for contribution to knowledge and correction as well as the final draft approval.

OGB Nwaorgu was involved in the study design, performed ABR testing, data collection, manuscript review for contribution to knowledge and correction as well as the final draft approval.

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OO Akinyinka was involved in the study concept and design, manuscript drafting and review for contribution to knowledge and correction as well as the final draft approval.

Design—A cohort audiometric study of newborns between October 2012 and April 2013.

Settings—Secondary and tertiary hospital based study.

Participants—Consecutive 126 HIV-exposed and 121 HIV-unexposed newborns.

Intervention—Hearing screening of the newborns were done with Auditory Brainstem Response and compared with maternal HAART, CD4 cell counts, RNA viral loads and newborn CD4 percent.

Main outcome measure—Hearing threshold levels of both groups were measured and analyzed.

Results—11.1% of HIV-exposed and 6.6% of unexposed newborns had hearing impairment ($p=0.2214$). 6.4% of HIV-exposed and 2.5% HIV-unexposed newborns had hearing threshold $>20\text{dBHL}$ ($p = 0.1578$). There was no significant association between the hearing thresholds of HIV-exposed newborns and maternal CD4 cell counts ($p = 0.059$) but there was with maternal viral load ($p=0.034$). There was significant difference between the hearing thresholds of HIV-exposed newborns with CD4 % of ≤ 25 and >25 . This study showed significant difference in the hearing of the 119 HAART-exposed newborns and 7 unexposed newborns ($p=0.002$; $RR=0.13$ [$0.05-0.32$]).

Conclusion—There was a trend towards more hearing loss in HIV-exposed newborns. However, hearing thresholds increase with increasing mothers' viral load. This background information supports the need for further studies on the role of *in-utero* exposure to HIV and HAART in newborn hearing loss.

Keywords

Auditory brainstem response; CD4 cell counts; hearing loss; hearing threshold; HIV viral loads

Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is a disease of public health importance with a significant burden on the quality of life of the affected individuals and national economy [1–5]. In 2009, an estimated 370,000 infants contracted HIV infection during the perinatal and breastfeeding period [6, 7]. AIDS related deaths are decreasing globally mainly due to the increased availability of highly active antiretroviral therapy (HAART) as well as care and support for people living with HIV/AIDS [8, 9]. The risk of vertical transmission of HIV between mother and child varies significantly between $<1\%$ to 25% [10–13]. The wide transmission variability may be due to maternal viral load, antiretroviral therapy (ART) administration to the mothers, presence of co-existing infections such as tuberculosis, hepatitis B virus, hepatitis C virus, gestational age at which the fetus is exposed to the virus and the evolution of the virus under the maternal immune pressure [14, 15]. The prevalence of paediatric HIV infection in France was $< 1\%$ [16] and South Africa was 7.5% [17], however a prevalence of 10% has been reported for paediatric HIV infection in Nigeria [18].

Hearing loss is a significant global health problem [19, 20] with significant impact on speech and language development, emotional status, social life, education as well as ultimate employability of the child in future especially in low and middle income countries such as Nigeria [19–25]. The aetiology of hearing loss in the newborn include mitochondrial abnormalities, genetic or congenital malformations, neurologic disorders or damage secondary to congenital infections such as cytomegalovirus (CMV), toxoplasmosis, rubella [26–30]. Others are intrauterine exposure to ototoxic medications [26–30] and HIV infection [19, 31–33].

In most resource-limited countries, there is no universal hearing screening for newborns and hearing loss is infrequently detected at an age when language acquisition would have passed. In Nigeria the only newborn hearing screening showed 6.5% hearing impairment [24] while 2.8–14.5% hearing impairment was found in Nigerian infants and/or elementary school children [21, 23, 25]. Though the co-existence of HIV/AIDS infection and hearing loss may significantly impact the child's quality of life, studies have also shown that some antiretroviral medications are associated with tinnitus and hearing loss [34]. There are also reports of hearing impairment in adults and children receiving antiretroviral medications [35, 36]. In particular, nucleoside reverse transcriptase inhibitor class of ART is associated with hearing loss in perinatally HIV-infected children because of its mitochondrial dysfunctional effect [37, 38]. There is however limited knowledge on the effect of HIV and antiretroviral medications on the integrity of hearing of the exposed newborns in sub-Saharan Africa where the disease is prevalent. Early identification of hearing impairment, by any electrophysiological audiometric tests, with appropriate intervention or rehabilitation will reduce the period of auditory deprivation leading to an improved speech and language development. Therefore, this study determined the prevalence of sensorineural hearing loss among HIV-1 exposed newborns as well as the association between their hearing threshold and maternal RNA viral load, CD4 cell counts and HAART administration.

Methods

Study design

This was a cohort audiometric study of newborns in Ibadan, Nigeria involving consecutive HIV 1-exposed and HIV-unexposed newborns studied between October 2012 and April 2013. The study was approved by the Joint University of Ibadan/University College Hospital, Ibadan, Nigeria Ethical Review Committee and informed consent was obtained from each parent.

Sampling method

All the consecutive newborns of mothers during the study period at the two study locations were recruited. Inclusion criterion was a live healthy newborn aged 1 month while ill newborns were excluded from the study. The HIV-exposed were newborns of HIV-1 infected mothers while the HIV-unexposed were newborns of HIV-uninfected mothers. HIV-exposed newborns were recruited from the postnatal HIV clinics at the University College Hospital, Ibadan and Adeoyo Maternity Hospital, Ibadan, Nigeria supported by the President's Emergency Plan For AIDS Relief (PEPFAR) and AIDS Prevention Initiative

Nigeria (APIN) while the HIV-unexposed newborns were recruited from the immunization clinics of the same hospitals. HIV screening and Venereal Disease Research Laboratory (VDRL) tests are routine for mothers at the antenatal clinics of these hospitals.

Data collection procedures and interventions

Structured questionnaires

A structured questionnaire detailing family socio-demographic data and risk factors associated with hearing loss in the newborns was administered to each mother. Clinic records documenting types of HAART, time of commencement of HAART in relation to the index pregnancy and the duration of therapy by mothers were retrieved.

Virology and Immunology

Blood sample was collected from all the HIV-exposed newborns for HIV-DNA PCR, CD4 cell count and CD4% determination at the Virology Laboratory of University College Hospital, Ibadan. The mothers' HIV status, VDRL test result, and the last CD4 cell count (cells/mm³) and RNA viral load (copies/ml) determined during the pregnancy of the index newborns were retrieved from their antenatal records kept at the PEPFAR/APIN clinic records unit. The protocol of the study centres included determination of the CD4 cell count and plasma viral loads of HIV infected mothers at every three months in pregnancy. CD4 cell count and CD4% (percentage of lymphocytes that are CD4+) were determined using the Partec (Munster, Germany) CD4 easy count and CD4% easy count kits respectively. Both assays were based on the principle of no lyse, no wash. HIV-DNA detection (for early infant HIV diagnosis) and HIV-RNA quantification were done using the Roche HIV-DNA and HIV-1 RNA Amplicor version 1.5 respectively. The lower and upper detection limits of the HIV viral load assay are 400 copies/ml and 750,000 copies/ml of plasma respectively.

Auditory brainstem response (ABR) test

The Auditory Brainstem Response (ABR) audiometry was performed on all the participants in the Audiology Booth of the Audiology Unit of the Department of Otorhinolaryngology, University College Hospital (UCH), Ibadan. Hearing thresholds after sedation with chlorhydrate (70mg/kg) were estimated with automatic ABR-test system (MAICO MB 11 Classic (by MAICO Diagnostic GmbH, Salzufer, Berlin, Germany). Disposable electrode sticky pads one each were attached to the top of the forehead (vertex), the right and left mastoid regions and appropriate sized ear tips were inserted into the ear canals. The ABR waveforms were generated after an automated click stimulus was presented mono-aurally to each tested ear. Both ears were tested. The hearing screening was electronically reported as pass (no impairment of hearing) if there was response at a test level of 35dB or refer (presence of hearing impairment) if there was no response at 35dB. To obtain the participants' estimated hearing threshold levels in this study, both standard and Time Step Stimulus ABR tests were performed. Time step stimulus uses "packets" of 6 clicks following each other very rapidly in which the intensity increases in 10 dB increments for each click in the packet. The entire click packets were presented in 25ms. The maximum output of the click stimulus was 70 dB. ABR threshold was defined as the lowest stimulus level where wave V was still present and reproducible and was determined in 10 dB steps. In

this study, hearing impairment was defined as hearing threshold $> 20\text{dBHL}$ at frequencies of 1 KHz to 8 KHz.

Data analysis

The demographic variables of age, sex, parent's level of education, occupation, income, family history of hearing loss, use of ototoxic medication in pregnancy and the duration of use, birth asphyxia, body rashes in mothers during pregnancy, cleft lip/palate for the HIV exposed newborn were compared with the data from HIV unexposed newborns. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Version 17. Proportions were compared using Chi-square with Yates' correction or Fisher's exact tests. Normally distributed, continuous variables were compared by Student's *t*-test for independent group. The association between hearing threshold of the HIV-exposed newborns and their mother's RNA viral load and CD4 cell count level as well as HAART administration was tested with Pearson Chi-square. Level of significance was determined at $p < 0.05$, two-tailed level at 95% Confidence Interval (CI) and correlation coefficient (*r*). We calculated a sample size of 98 using estimated prevalence of hearing loss of 4.1% in HIV-exposed newborns and 1.2% in HIV-unexposed newborns, putting into consideration 20% attrition rate, the minimum sample size was further increased to 120 in each category.

Results

Socio-demographic and clinical characteristics

One hundred and twenty six (126) HIV-exposed newborns comprising 72 (57.1%) males and 54 (42.9%) females and 121 HIV-unexposed newborns comprising of 69 (57%) males and 52 (43%) females were studied. The mean age of $2.87 \text{ weeks} \pm 1.05$ in HIV-exposed newborn and $2.84 \text{ weeks} \pm 1.04$ in HIV-unexposed newborns were similar ($p=0.868$). Risk factors of sensorineural hearing loss between the two groups were similar (Table 1). However, three (2.4%) HIV-exposed newborns have cleft palate compared with none in the unexposed group.

HIV infection was diagnosed in 87 (69%) mothers before the index pregnancy and 39 (31%) of the mothers were diagnosed HIV-infected during the index pregnancy at booking at the antenatal clinic. One hundred and nineteen (94.4%) mothers were on HAART for a duration ranging from 1 month to 123 months with a mean duration of 27.14 ± 27.4 while 7 (5.6%) mothers were not on HAART. Ninety-two (73.02%) mothers were on combination therapy with nevirapine, lamivudine and zidovudine, 21 (16.67%) were on combination of efavirenz, lamivudine and tenofovir, 4 (3.17%) were on combination of (atazanavir + ritonavir), tenofovir, zidovudine and lamivudine and 2 (1.59%) mothers were on other combination therapies which included lopinavir or abacavir. All the mothers in this study believed that their newborns can perceive sound. The comparison of HIV exposed newborns with and without hearing loss are shown in table 2.

Immunology

There is no statistically significant difference between the mean CD4 count of mothers of HIV-exposed newborns with hearing impairment and those without hearing impairment ($p=0.13$). The CD4 cell % of the HIV-exposed neonates ranged from 9.5 – 86.8% with a mean of $36.06 \pm 14.85\%$, median of 33.70%. Ninety-seven (77%) HIV-exposed newborns had CD4 percentage $> 25\%$ and no correlation between the CD4 cell % of the newborns and their mothers' CD4 cell count was demonstrated ($p = 0.99$, $r = 0.001$).

Virology

None of the HIV-exposed newborns tested positive to HIV-1 by DNA PCR. The RNA viral load of 400 copies / ml was regarded as non-detectable. Sixty two (49.2%) mothers had detectable RNA viral load with values ranging from 490 – 767,012 copies / ml with a median of 12,183. There is also no significant correlation between the RNA viral load of these HIV infected mothers and duration on HAART ($p= 0.61$; $r=0.04$).

Auditory brainstem response test

In the HIV-exposed and -unexposed groups, there was more referred hearing in the left ear than the right ear (Table 3). More HIV-exposed newborns had hearing loss (11.1%) than the HIV- unexposed newborn (6.6%) but the difference is not statistically significant ($p = 0.2214$). 6.4% of HIV-exposed newborns had hearing threshold $> 20\text{dBHL}$ compared with 2.5% of HIV unexposed newborns ($p = 0.1573$) in the right ear with similar findings in the left ear (Table 3). Five of the 14 HIV-exposed newborns with sensorineural hearing loss were from mothers not on HAART. Six (42.9%) of the 14 HIV-exposed newborns with hearing loss had CD4 percentage of ≤ 25 while 14 (12.5%) of the remaining 112 HIV-exposed newborns had CD4 % ≤ 25 . There was a statistical significant difference in the right and left hearing thresholds of HIV-exposed newborns with CD4 percentage of ≤ 25 compared with those with CD4 percentage > 25 ($p = 0.047$; $p = 0.043$ respectively). There was a strong association between the hearing threshold of the HIV-exposed newborns and CD4 cell counts of their mothers ($r=0.62$) but the relationship is not significant ($p = 0.059$). There was a statistically significant relationship between hearing threshold of the HIV-exposed newborns and their mothers' viral load count ($p=0.034$).

There was a significant difference in the hearing of the 119 exposed newborns whose mothers were on HAART and those of the 7 HIV-exposed newborns whose mothers were not ($p=0.002$; RR 0.13 95% CI 0.05 – 0.32). There was no significant difference in the right and left hearing threshold of newborns exposed to nevirapine containing HAART *in-utero* and those not exposed ($p=0.303$; $p=0.263$ respectively) and there was no difference in the right and left hearing threshold of newborns exposed to efavirenz containing HAART *in-utero* and those not exposed ($p=0.481$; $p=0.359$ respectively).

Discussion

Neonatal detection of hearing loss and early intervention should be the standard of care in any country including Nigeria. Though the cause of hearing impairment is multifactorial in babies, the contribution of HIV/AIDS and exposure to antiretroviral medications *in-utero* in

HIV-exposed newborns was investigated in this study. This study reports the first determination and comparison of hearing status in HIV-exposed and -unexposed newborns in sub-Saharan Africa where the burden of the disease is high.

The strength of this study is the thorough hearing evaluation performed on both the HIV-exposed and -unexposed newborns. Additional strength of this study is the detailed information on HIV status of the mothers which was related with the hearing threshold of the HIV-exposed newborns. In this study, there was a trend towards more hearing loss in newborns exposed to maternal HIV *in-utero* (11.1%) than newborns not exposed to maternal HIV (6.6%) but this did not reach significance ($p=0.217$). This confirms that hearing impairment in newborns starts soon after birth [24, 39]. A previous Brazilian hearing screening of infants born to HIV-seropositive mothers had reported a prevalence of 10% but found no association between HIV exposure during pregnancy and hearing loss [39]. The difference between the report of this present study and Manfredi et al may be due to the different electrophysiological tools used in the two studies. While Manfredi et al utilized Oto-Acoustic Emissions (OAEs) which measures cochlear functions and ABR measures the function of the auditory pathways for vestibulocochlear nerve, both instruments have however been successfully used in hearing screening of newborns. To prevent this disparity, the Joint Committee on Infant Hearing recommended a method of two-step automated otoacoustic emission (OAE) program, completed by an ABR for the positive diagnosis of hearing impairment in all newborns at risk of hearing impairment [40]. Though, using the two electrophysiologic tests of hearing tools for routine hearing screening is unaffordable in Nigeria, however it has been reported that click ABR in babies referred for newborn hearing screening can predict the degree of hearing loss in them [41] which was therefore used in the present study.

The high prevalence of sensorineural hearing loss found in this study supports the need for routine hearing screening for newborns. Although 6.4% HIV-exposed newborns had mild hearing loss as compared to 2.5% in the non-exposed group, this difference was not significant, however, the mild sensorineural hearing loss has been reported to interfere with language, education and psychosocial development of a child later in life [24, 33]. Sensorineural hearing loss distorts auditory signals as it leaves the cochlea to be processed at higher auditory center thereby incapacitating the development of communication ability of the affected individual.

The trend towards higher prevalence of sensorineural hearing loss (SNHL) among the HIV-exposed newborns compared with the unexposed group may have association with the maternal HIV status. Vertical transmission of HIV from infected mothers to their fetuses or newborns has been documented [42, 43]. In Europe and United States of America, mother-to-child transmission has almost been eliminated but it is still a problem in developing countries [44]. In the UK, HAART reduced the rate of HIV maternal-to-child transmission from 25.6% in 1993 [45] to 1.2% between 2000 and 2006. The rate was further reduced to 0.1% in mothers with undetectable viral load [46]. The HIV-DNA PCR tests performed on the participants at the neonatal period were negative for HIV-1 probably because the HAART used in pregnancy prevented transmission of HIV from the mothers to their babies. It is also possible that the hearing impairment in the five of the seven newborns of mothers

who were not on ART may be associated with the *in-utero* effect of the virus; however, all the newborns were seronegative for HIV 1 at birth. Passive exposure to HIV-1 proteins in the absence of actual infection, or exposure to a pro-inflammatory environment during gestation may have contributed to the observed effects on hearing threshold. HIV has been known to cause hearing impairment by attacking directly the cochlear and vestibulo-cochlear nerve [47]. The possibility of neurotropism of HIV in a developing brain causing peripheral and central hearing alteration has also been documented [47, 48].

The limitation of the study is the inability to assess for toxoplasmosis and other viral infection such as cytomegalovirus, toxoplasmosis and rubella known to cause hearing loss. None of the mothers had a positive VDRL. The ototoxic and vestibulotoxic side effects of some HAART medications have been reported [35, 36] but the information on these side effects in HIV-exposed newborns is rare. Hearing loss has been reported in HIV infected individual on stavudine, lamivudine and Efavirenz [49] but not in those on zidovudine and didanosine [50]. However, there is no information on the hearing of HIV exposed newborns who were exposed to any of these medications in-utero. Inference from the present study demonstrated that there is lesser risk of hearing loss among newborns exposed to HAART *in utero* ($p=0.002$; $RR=0.13$), this trend can only be confirmed by a larger study on the role of HAART in the development of SNHL.

The CD4 cell count and CD4 % which measure the degree of immunosuppression in HIV-infected patients is used in staging and monitoring disease, deciding when to commence therapy, defining the risk for mother to child transmission and determining treatment failure [51–53]. This study showed significant association between the CD4 cell % and hearing threshold of HIV-exposed newborns. Those with CD4 cell % of ≤ 25 had higher hearing threshold than those with $>25\%$. Therefore, CD4 percentage may be a useful predictor of hearing level in HIV-exposed newborns. There was a significant relationship between high maternal viral load as measured by HIV-RNA copies / ml and higher hearing threshold levels in HIV-exposed babies. This suggests that HIV virus in mothers might have effect on the sensory organ of hearing and/or the vestibulo-cochlear nerves of their newborns causing hearing loss, but this is difficult to postulate in the absence of HIV infection in the newborns. A larger population study would verify this observation and determine the role of the mothers' RNA viral load in predicting the hearing threshold of their babies.

One would expect that a short duration of HAART is associated with high RNA viral load seen in HIV-infected patients, however there is no significant correlation between duration of antiretroviral treatment and RNA viral loads in this present study. Non-adherence to antiretroviral medications may be a possible factor for the high RNA viral load and mothers need to be adequately educated on the importance of regular intake of HAART medication on their health and babies.

Despite the observation in this study, other studies have shown that the hearing threshold of babies can change during infancy [54]. Since auditory system of newborns might not have developed fully at birth [55], a repeat of the hearing evaluation/assessment with electrophysiological hearing test later in infancy should confirm persistence, improvement or worsening of hearing loss thereby necessitating timely treatment or rehabilitation with

either hearing aid or cochlea implant in order to improve acquisition/development of normal speech and hearing. With the introduction of HAART, HIV-exposed or -infected newborns now live longer and have better quality of life and therefore, the need for later evaluation of hearing is imperative.

Conclusion

Hearing loss is present in both the HIV-exposed and -unexposed newborns and there is a trend of higher prevalence of sensorineural hearing loss in HIV-exposed newborns than in HIV-unexposed newborn. Routine hearing screening is therefore recommended to identify early newborns with hearing loss in all newborns including the HIV exposed newborns. In addition, there is a reduced risk of developing hearing loss in newborns exposed to HAART *in-utero* than those who were not. This finding needs further verification in a similar comparative study with higher sample size of HIV exposed newborns not exposed *in-utero* to HAART.

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Table 1

Risk factors for hearing loss in the participants

Variables		HIV exposed newborns	Non-HIV exposed newborns	Level of significance (p < 0.05; 95%CI)
Family history of hearing loss	Yes	17 (13.5%)	15 (12.4%)	0.798
	No	109 (86.5%)	106 (87.6%)	
Gestation at delivery	37weeks	123 (97.6%)	118 (97.5%)	0.967
	< 37weeks	3 (2.4%)	3 (2.5%)	
Birth weight (Range) (Mean)		2.5 – 4.7kg	2.5 – 4.6kg	0.863
		4.32±0.90	4.34±0.89	
Birth asphyxia	Yes	2 (1.6%)	2 (1.7%)	0.685
	No	124 (98.4%)	119 (98.3%)	
Body rashes in mothers during first trimester of Index pregnancy	Yes	124 (98.4%)	120 (99.2%)	0.959
	No	2 (1.6%)	1 (0.8%)	
Exposure to non HAART ototoxic medication	Yes	0	0	0.819
	No	112 (88.9%)	108 (89.3%)	
	Not sure	14 (11.1%)	13 (10.7%)	

Table 2

Comparison of characteristics of HIV exposed newborns with and without hearing loss

Variables		HIV exposed newborns with hearing impairment	HIV exposed newborns without hearing impairment	Level of significance (p < 0.05; 95% CI)
Population size		14 (11.1%)	112 (88.9%)	
Socioeconomic class	Low	9 (64.3%)	69 (61.6%)	0.485
	Middle	4 (28.6%)	31 (27.7%)	
	High	1 (7.1%)	12 (10.7%)	
CD4 cell percentage (%)	Range	15.8 – 52.6	9.5 – 86.8	0.092
	Mean±SD	32.7±13.9	36.1±14.8	
Mother's viral load (copies per ml)	Range	672 – 767,012	490 – 380,882	0.001
	Mean±SD	71,678±46.27	55,611±16.5	
	Median	3244		
Mother's CD4 count (cells/mm ³)	Range	171 – 883	20 – 1552	0.13
	Mean±SD	423±231.7	442.22±175.11	

Table 3

Comparison of ABR hearing screening outcome and hearing thresholds of the HIV exposed and non-exposed newborns

Variable	Hearing level (dB)	HIV exposed newborns	Non-HIV exposed newborns	Level of significance ($p < 0.05$; 95%CI)
Hearing screening outcome				
<i>Right ear</i>	Refer	12 (9.5%)	6 (5%)	0.1771
	Pass	114 (90.5%)	115 (95%)	RR=1.9206 (0.7445–4.9549)
<i>Left ear</i>	Refer	14 (11.1%)	8 (6.6%)	0.2214
	Pass	112 (88.9%)	113 (93.4%)	RR=1.6806 (0.7313–3.8621)
Hearing threshold				
<i>Right ear</i>	20dBHL	118 (93.6%)	118 (97.5%)	0.1573
	> 20dBHL	8 (6.4%)	3 (2.5%)	RR=2.5608 (0.6956–9.4272)
<i>Left ear</i>	20dBHL	118 (93.7%)	118 (97.5%)	0.1573
	> 20dBHL	8 (6.3%)	3 (2.5%)	RR=2.5608 (0.6956–9.4272)