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Can Transient Evoked Otoacoustic Emissions be used to Monitor the Hearing of HIV-Infected Patients? A Case-Control Study in a Cameroonian Population

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Abstract

Background: Many studies suggest a deleterious effect of Human Immunodeficiency Virus and its drugs on hearing and advocate for a close monitoring. We assessed the utility of Transient Evoked OtoAcoustic Emissions (TEOAEs) for the screening of preclinical hearing damage among HIV-infected patients.

Methods: We conducted a case-control study in the Yaoundé NSIF Hospital. Ninety HIV-positive cases and 90 HIV-negative controls aged 15 to 49 years without prior history of hearing loss-causing disease or drug were included. Hearing loss was defined as a mean pure tone audiometry (PTA) threshold ≥35 dB and TEOAEs were recorded.

Results: PTA revealed 15 cases with hearing loss≥ 35 dB (16.67%) versus 2 among the controls (2.24%, p=0.002).There were 22 and 3 fail TEOAEs in the case and control groups respectively. The cases were 10.9 (95% CI: 3.24-36.46) times more likely to have Fail TEOAE than the controls. The performances of TEOAE test were: sensitivity 80% vs. 100%, specificity 90% vs. 99%, positive predictive value 42% vs. 66% and negative predictive value 98% vs. 100% respectively in the HIV-positive and HIV-negative groups.

Conclusion: TEOAEs could be a useful to detect preclinical hearing impairment in HIV-positive patients with normal pure tone audiometry. In addition, it's an easy and noninvasive procedure.

Keywords: Hearing loss; HIV infection; Transient Evoked Otoacoustic Emissions (TEOAE); Ototoxicity, Pure tone audiometry

Abbreviations: 3TC: Lamivudine; ZDV: Zidovudine; NVP: Nevirapine; LPV/r: Lopinavir+ritonavir; TDF: Tenofovir; EFV: Efavirenz; DDI: Didanosine; ABC: Abacavir; HIV: Human Immunodeficiency Virus; HL: Hearing Loss; RE: Right Ear; LE: Left Ear; HAART: Highly Active Antiretroviral Therapy; NA: Not applicable; HAART: Highly Active Antiretroviral Therapy

Introduction

Human Immunodeficiency virus (HIV) is a global challenge. According to the Joint United Nations Program for HIV/AIDS (UNAIDS), 35 million persons were living with it by the end of 2013, of whom 24.7 million (71%) in sub-Saharan Africa [1]. Nowadays, the access to Highly Active Anti-Retroviral Therapy (HAART) not only allows a longer life of affected patients, but leads to the rise of previously underreported diseases. There is a rising concern that both HIV and HAART may damage the ear. According to the US National Institute of Health, as much as 75% adults with AIDS have some kind of hearing disorder [2]. The majority of those hearing losses are sensorineural and one of their supposed mechanisms is the mutations occurring in the mitochondrial DNA and accumulating eventually in the cochlea [3]. Other mechanisms include the neurotropism of HIV and the ototoxicity of some antiretroviral drugs [4]. It is important to detect hearing impairment before it emerges clinically, in order to take appropriate measures on time, especially in Sub Saharan Africa which shelters the majority of those patients. To this purpose, there are several methods including otoacoustic emissions (OAEs), first described by Kemp in 1978 and most used worldwide for the screening of newborns [5-7]. Another modality is the Distorsion Product Otoacoustic Emissions (DPOAEs) which complements the previous. While TEOAEs give a response valid in the 1-4 kHz frequency range, DPOAEs cover the high frequency range up to 10 kHz. But DPOAEs are more suited for investigation since its analysis and interpretation are difficult [8]. TEOAEs could help monitoring HIV-patients, both those with and without HAART. In fact, many authors emphasize the necessity of such a follow up [4,6,9]. We aimed to assess the performance of TEOAEs in the diagnosis of hearing loss in HIV-infected patients.

Patients and Methods

Study population and setting

We conducted a case- control study in patients aged 15 to 49 years in the Hospital of National Social Insurance Fund (NSIF) in Yaounde between March 1st 2012 and January 31st 2013. HIV positive patients (cases) were selected from the Registered Center for Treatment of HIV patients, from the Otolaryngology (ORL) service or from outpatient clinics and Internal medicine. The HIV test in the Hospital was done in two steps: a rapid screening test (Determine®), followed by a confirmation test for samples screened positive (ELISA or Western blot). HIV-negative patients were selected from outpatient clinics, ORL service or laboratory after a negative HIV test. In addition, we excluded any patient with present or past history of treatment with traditional medicine or known ototoxic drug taken less than 3 months prior to the study, family history of hearing loss, occupational exposure to noise, any condition leading to hearing loss by itself or by its treatment (syphilis, tuberculosis, otitis, meningitis, stroke, chemotherapy for cancer, pneumocystosis, neuromeningeal cryptococcosis, diabetes, Hypertension, malaria) and ear surgery whatever the indication. We recruited a total of 180 patients, of whom 90 were HIV-negative (controls) and 90 HIV-positive (cases). The latter were divided into 3 subgroups: 30 ARV Naïve patients, 30 under first line HAART and 30 under second line HAART. The first and second line HAART regimens are defined by the WHO guidelines [10] and applied by the National Aids Control Committee (NACC) through its registered treatment centers. The first line regimens were fixed dose combinations made of three of the following molecules: lamivudine (3TC), zidovudine (ZDV), efavirenz (EFV), tenofovir (TDF) and nevirapine (NVP). The second line regimens, in addition to the above mentioned molecules (except EFV and NVP) could combine abacavir (ABC), ritonavir-boosted lopinavir (LPV/r) or didanosine (ddI) in the tritherapy. The distribution of HAART regimens is shown in Table 1.

Subgroup	Regimens	N (%)
HAART Naïve	None	30 (33.34)
1st line	3TC-ZDV-NVP	23 (25.56)
	3TC-ZDV-EFV	5 (5.55)
	TDF-3TC-NVP	1 (1.11)
	TDF-3TC-EFV	1 (1.11)
2nd line	TDF-3TC-LPV/r	13 (14.45)
	3TC-ZDV-LPV/r	9 (10)
	3TC-ABC-LPV/r	2 (2.22)

2nd line	3TC-ZDV-ABC	2 (2.22)
	TDF-ZDV-LPV/r	2 (2.22)
	3TC-ddI-LPV/r	1 (1.11)
	ZDV-ddI-LPV/r	1 (1.11)
TOTAL		90 (100)

Table 1: Distribution of the Highly Active Antiretroviral Therapy regimens in the HIV positive group.

We did an ORL examination with microscopy of the ear, cleaning the external auditory canal when necessary. In patients with macroscopically normal external and middle ear, we performed an impedancemetry with the *AT235* device (Interacoustics, Assens, Denmark) and did not include subjects with abnormal middle ear function. Then we also performed a pure tone audiometry (PTA) in a soundproof box, looking for the thresholds on frequencies 0.125 to 8 kHz on air conduction, and 0.25 to 8 kHz on bone conduction, with the *A33* device (Interacoustics, Assens, Denmark). The mean pure tone average was calculated according to the formula of BIAP (Bureau International d'audiophonologie):

$$\left(T_{0.5}+T_1+T_2+T_4\right)\div 4$$

T_x being the threshold at x frequency [11].

We considered hearing loss as a mean pure tone average ≥35 dB HL. This threshold is comprised in the normal cochlea sensitivity range which is 20 to 40 dB [12]. In fact, TEOAEs disappear if the hearing threshold rises up to 30 dB and above [5,13]. The TEOAEs were recorded using the ILO 292 USB device (OtodynamicsLtd, Hatfield, UK), running the ILOV6 software in diagnostic mode. The data recorded were the intensity and reproducibility of the response on the frequency range (1, 1.5, 2, 3 and 4 kHz). The subjects were tested with evoked clicks at an intensity between 80 and 85 dB SPL (sound pressure level) delivered through ear probes. The test result was pass when we elicited a reproducibility of at least 50% and positive TEOAEs on at least three of the frequencies. Otherwise the result was Fail and the patient was retested twice and the best result retained.

The data collected were analyzed with the SPSS 14.0 for Windows (SPSS, Chicago, Illinois, USA). We described continuous variables using means and standard deviations (SD), and categorical variables using their frequencies and percentages. The Student's *T* test was used to compare means between the subgroups. To calculate the performances of the TEOAE test, we set the gold standard as the result of PTA (hearing loss= pure tone average ≥35dB HL). Fail TEOAE was the positive result and Pass the negative result. Odds ratios were used to compare the probability of hearing loss amongst the subgroups. A p value <0.05 was considered statistically significant. The protocol of this study was approved by the Ethics committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I. Each patient or parent had to give his agreement by signing an informed consent form.

Results and Analysis

We recruited 180 patients (360 ears). They were 129 women representing 71.66% (60 HIV-negative, 22 HAART-Naïve, 23 1st line HAART and 24 2nd line HAART).The overall mean age was 33. 41 (SD=7.72) years. It was 35.31 (SD=7.78) years in the HIV-positive group and 31.51 (SD=7.21) years in the HIV-negative group (p=0.07).The general characteristics of the cases are summarized in Table 2. The pure tone audiometry (PTA) revealed 15 cases (16.67%) of hearing loss ≥ 35 dB among the HIV positive patients versus 2 (2.23%) among the HIV negative controls (p=0.002). There were 22 cases (24.45 %) of Fail TEOAEs in the HIV-positive group (of whom 6 were bilateral), versus 3 unilateral (3.33 %) in the controls (p=0.002). Of the hearing losses, 11 were sensorineural (73.4), 3 mixed (20%) and 1 of transmission (6.66%). Forty per cent were left sided, 26.7% right sided and 33.3% bilateral. The distribution of patients according to PTA and OAEs is given on (Table 3).

The mean intensity of TEOAEs was 13.6(SD=4.35)/12.5(SD=8.36) for the controls, 9.1 (SD=12.94, p=0.07)/6.4(SD=16.55, p=0.05) for the HAART naïve, 9.2(SD=7.26, p=0.003)/7.5(SD=12.77, p=0.014) for the 1st line HAART and 11.2(SD=13.06, p=0.32)/8.6(13.3, p=0.14) for the 2nd line HAART in the right and left ear respectively. The mean reproducibility was 92.9(SD=7.87)/92.2(SD=12.24) for the controls, 83.3(SD=25.43, p=0.05)/80.0(SD=27, p=0.02) for the HAART Naïve, 83.3(SD=22.75, p=0.02)/80.1(SD=26, p=0.02) for the 1st line HAART and 86.2(SD=24.31, p=0.15)/85(SD=21.37, p=0.08) for the 2nd line HAART in the right and left ear respectively. We got 12/2 true positives, 16/1 false positives, 3/0 false negatives and 149/177 true negatives in the HIV-positive/HIV-negative patients respectively (results in ears). The sensitivity of TEOAE test was 80/100%, specificity 90/99%, positive

predictive value (PPV) 42.8/66% and Negative predictive value (NPV) 98/100% for cases/controls respectively.

			Subgroup			Total N (%)
		HIV-	HIV+			
			HAART -	1st Line	2nd Line	
HIV Discovery	< 1 year	NA	19	1	1	21 (23.33)
	1-5 years		9	18	17	44 (48.89)
	>5 years		2	11	12	25 (27.78)
Type of HIV	Unknown	NA	19	16	14	49 (54.45)
	Type 1		11	13	16	40 (44.44)
	Type 2		0	1	0	1 (1.11)
CD4 range	< 200	NA	16	3	7	26 (28.89)
	200 - 499		12	19	15	46 (51.11)
	≥500		2	8	8	18 (20)
WHO stage	I	NA	10	3	5	18 (20)
	II		10	16	13	39 (43.34)
	III		9	11	12	32 (35.55)
	IV		1	0	0	1 (1.11)
Duration of HAART	< 1 year	NA	-	3	2	5 (5.55)
	1-5 years		-	19	17	36 (40)
	>5 years		-	8	11	19 (21.11)
Mean CD4 count (SD)		NA	204.86 (181.7)	431.16 (267.7)	393.66 (270.1)	343.23 (260.4)
Total Number		90	30	30	30	-

Table 2: General characteristics of the patients.

	HL ≥ 35 dB		Fail OAE	
	RE	LE	RE	LE
HIV negative	0	2	1	2
HAART Naïve	3	0	5	4
1st line HAART	3	4	4	6
2nd line HAART	2	3	3	6

Table 3: Distribution according to pure tone audiometry (PTA) and TEOAE results.

HIV-infected patients were 10.9 times (CI 95% 3.24-36.46, p = 0.03) more likely to have Fail TEOAE than the HIV-uninfected ones. This was the case in all the HIV positive subgroups, from the HAART-Naïve patients (OR: 16.7 , 95% CI 11.4-20.1, p =0.01 for the right ear and OR: 6.7 , 95% CI 3.5-9.8, p =0.03 for the left ear) to 1st line cases (OR: 14.3, 95% CI 7.6-19.5, p =0.02 for the right ear and OR: 11.2, 95% CI 7.1-20.3, p =0.005 for the left ear), and 2nd line cases (OR: 10.0, 95% CI 4.5-13.9, p =0.05 for the right ear and OR: 11.2, 95% CI 7.1-20.3, p =0.005 for the left ear). We had 14 false positive patients (16 ears) in the HIV-positive group and 1 in the HIV-negative one. Their characteristics are summarized in Table 4. We noticed that most of them had no audiological complaint (57.14% of cases), had been diagnosed more than a year ago (71.42%) and were in advanced WHO stages of the disease (50% in stages III-IV). Univariate analysis failed to link the age, the sex, the duration of treatment or CD4 count to hearing loss on PTA or TEOAE.

	Group	Age	Sex	Side[a]	WHO stage	Complaint	HIV Duration	CD4	Mean HL (dB)	HAART Regimens
1	Naïve	48	F	R	III	Hearing loss, tinnitus	< 1 year	327	15	-
2	Naïve	37	F	R	I	None	< 1 year	288	11.25	-
3	Naïve	34	F	L	IV	Hearing loss	< 1 year	219	33.75	-
4	Naïve	34	F	L	III	None	1-5 yrs	33	33.75	-
5	Naïve	45	M	L	III	None	< 1 year	22	30	-
6	Naïve	38	M	L	III	Hearing loss, Pruritus	1-5 yrs	255	30	-
7	1st line	39	M	R	II	None	1-5 yrs	223	21.25	3TC-ZDV-NVP
8	1st line	39	M	R	II	Tinnitus, otalgia	1-5 yrs	471	5	3TC-ZDV-NVP
9	1st line	49	F	B	II	Hearing loss, dizziness	1-5 yrs	364	20R/21.25L	TDF-3TC-NVP
10	2nd line	48	M	R	III	Hearing loss, dizziness	> 5 yrs	243	23.75	3TC-ZDV-LPV/r
11	2nd line	42	F	B	III	None	> 5 yrs	550	10R/15L	3TC-ZDV-LPV/r
12	2nd line	48	M	L	I	None	> 5 yrs	450	25	3TC-ddI-LPV/r
13	2nd line	40	F	L	II	None	1-5 yrs	356	21	3TC-ZDV-LPV/r
14	2nd line	37	F	L	II	None	> 5 yrs	397	12.5	TDF-3TC-NVP
15	HIV-	32	F	R	-	None	-	-	5	-

a: R= right, L= left

Table 4: Characteristics of false positive patients.

Discussion

The damage to ear and hearing by HIV and HAART is an increasing concern among audiologists, who emphasize on the necessity to properly monitor the hearing of HIV-infected patients. To do so, the ideal test would be an easy to do, easy to interpret, time sparing and pocket friendly. We aimed to study the performance of Transient Evoked Otoacoustic Emissions (TEOAEs) in that purpose. We found that HIV-infected patients had more hearing loss on Pure tone audiometry (PTA) and Fail TEOAEs than their HIV-negative counterparts. The sensitivity of TEOAE test in the study population was 80%, specificity 90%, positive predictive value (PPV) 42.8% and Negative predictive value (NPV) 98%, while for the controls, sensitivity was 100%, specificity 99%, PPV 66% and NPV 100%. Hearing loss on PTA was significantly more frequent among HIV-infected patients compared to HIV-

uninfected controls. Our findings support the fact already reported that HIV patients have more audiological manifestations than the general population. The neurotropism of HIV [14,15] and the ear toxicity of antiretroviral drugs [4,16] or those used to treat opportunistic infections [17] are the alleged causes. These reasons can also explain the poorer chance for the HIV-exposed patients to have normal TEOAEs as shown by the Odds Ratios. Forty per cent of hearing loss was left sided. To date, we have no explanation for this left side predominance which was also found by Khoza-Shangase [4].

The results of PTA, when compared to those of TEOAEs, reveal a gap between both tests, with an unexpectedly higher number of Fail TEOAEs and a great number of false positive TEOAEs. In fact this gap may reflect the superiority of TEOAE as screening test for preclinical hearing loss. This is consistent with the fact that 42.86% of those false positive had audiological complaints in spite of a good hearing on PTA. TEOAEs share this ability to reveal micro cochlear damage with DPOAE [18,19] but goes further in this purpose in adult patients as demonstrated by Kemp [8]. He explained that though complementary to each other, DPOAEs is less sensitive to minor and subclinical conditions in adults. In addition, DPOAEs recordings offer a lesser frequency specificity than TEOAEs [8]. The cases had significantly poorer TEOAE reproducibility and intensity compared to the HIV-negative controls, though this was only significant with 1st line patients in both ears for intensity and reproducibility, and Naïve patients in left ear for reproducibility. Both reproducibility and intensity may vary between subjects. But they remain remarkably constant in the same person, thus allowing to use them in the follow up of exposure to noise, drugs or diseases [20]. This assumes that their values reflect the strength of the cochlea. But the intensity is not a good reflect of the health of the cochlea since the coupling of the sensor with the patient and other non-auditory factors may influence it. So, it is more the presence of a detectable response than its intensity that makes TEOAE valid [8]. Then, the difference of intensity and reproducibility does not bear a great clinical importance.

The performance of TEOAE in literature varies greatly according to the study population (either general population or a group at risk). In a study of 4253 children of a universal screening program in Rhode Island State in the United States of America, sensitivity ranged from 81 to 100% and specificity from 70 to 99% in children. The positive predictive value ranged from 2.5 to 18%. The performances we obtained were good enough to envisage the use of this test clinically in the follow up of well targeted patients [5-7]. But the extensive use of TEOAE in adults is not usual. We failed to find a study similar to ours for comparison. Of the 14 HIV-infected false positive, 50% were at the late stages of the disease. In fact it is demonstrated that the worse the immune status, the worse the hearing [3]. It would be interesting to continue to follow those patients to see whether they develop clinical hearing loss on pure tone audiometry. Practically, to follow up HIV-patients with a normal pure tone audiometry, the physician may perform a TEOAE test. If the test comes positive, he must investigate factors like occupational or leisure exposure to noise, drug history and observance (including alternative medicines), comorbidities. Then he may give his patient counseling on diet and hygiene, rule out any ototoxic drug after concerting with the colleagues intervening on the same patient and/or prescribe another appropriate drug. This will be done especially if the patient has audiologic symptoms (tinnitus, pain, etc.). This study has some limitations. First, the study was limited to the 15-49 age range. The results could be different in children. However, Palacios, et al. [21] conducted a study on 23 HIV positive children aged 5 months to 16 years and receiving HAART, who displayed alterations in PTA and BERA, suggesting that HIV infected children under HAART are prone to hearing damage as well as adults are [21]. On the other hand early presbycusis could be responsible for hearing loss in some patients above 40 as it has been shown in some studies [22]. Secondly, the little size of the HIV subgroups gave little power to our analysis and finally we didn't follow the false positives to see whether they have a pathologic pure tone audiometry along the time. Thirdly, the hearing loss criteria, set at 35 dB is high since as from 26dB (mild hearing loss) TEOAEs can disappear. This can partially explain why there was less hearing loss on PTA compared to TEOAEs. Fourthly, TEOAEs do not detect auditory neuropathy and those patients, if any, would have been seen as Pass. For such patients, it is better to perform Brainstem Evoked Response Audiometry.

Conclusion

This study confirms the fact that HIV patients experience hearing loss more often than their HIV negative counterparts. Moreover, it shows the superiority of TEOAE over pure tone audiometry to detect preclinical hearing loss. If confirmed by other wider and deeper studies, these findings support the routine use of TEOAEs in the monitoring of the hearing of HIV-positive patients

since it is a rapid, noninvasive and pocket friendly test, especially in resource limited settings.

Summary

- HIV-positive patients experience more hearing losses than the HIV-negative ones, due to the neurotropic action of the virus the orototoxicity of anti-retroviral and anti-opportunistic infection drugs.
- It is important to monitor the hearing of those patients for early detection of any hearing loss in order to take appropriate measures.
- Pure tone audiometry is routinely used to this purpose. But an earlier diagnosis, when the damage is subclinical and the pure tone audiometry still normal is possible using otoacoustic emissions.
- Our results show that Transient Evoked Otoacoustic Emissions (TEOAEs) can be useful to early detect hearing loss in HIV population, with good performances compared to the pure tone audiometry. In addition, it is a cheap and non invasive test.

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