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Distortion Product Otoacoustic Emission Data in Perinatally HIV-Infected and HIV-Exposed but Uninfected Children and Adolescents in the Pediatric HIV/AIDS Cohort Study

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Abstract

The effect of perinatal HIV infection and exposure on sub-clinical auditory function can be measured with distortion product otoacoustic emissions (DPOAEs). DPOAEs were obtained at four frequency bins (1, 2, 3, and 4 kHz) and categorized by a signal-to-noise ratio. HIV infection was not associated with poorer DPOAEs. Among HIV-infected children, HIV viral load 400 copies/mL had significantly lower odds of better DPOAEs.

The measurement of distortion product otoacoustic emissions (DPOAEs) allows for an evaluation of underlying outer hair cell (OHC) function as a possible indicator of decreases in pure-tone hearing sensitivity (hearing loss)^{1,2} because the OHCs are vulnerable to essentially all cochlear insults, including ototoxicity and noise exposure. However, little research has been conducted to address the relationship between HIV exposure and OAEs. To date, there are no OAE data from children or adolescents with HIV exposure, although OAEs have been measured as a screen for hearing loss in newborns born to HIV-infected mothers,^{3,4}. Limited studies have been done in adults in which researchers specifically evaluated the effects of HIV infection on DPOAEs, but these studies reported no significant effect of HIV infection on DPOAEs.^{5,6}

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Recent data from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) suggested that children with perinatal HIV infection (PHIV) might have poorer hearing, as measured by pure-tone thresholds, than their perinatally HIV-exposed, but uninfected (PHEU) peers.⁷

Because hearing sensitivity is comprised of outer, middle, and inner ear function along with auditory neural function, the origin of such differences is unclear. More research is needed to determine the auditory mechanisms that lead to differences in hearing sensitivity. The purpose of this study was to evaluate OHC function specifically, as measured by DPOAEs, in PHIV and PHEU children.

METHODS

PHACS AMP is a prospective cohort study designed to evaluate the effects of perinatal HIV exposure, infection, and treatment on children and adolescents. PHACS AMP has 14 clinical sites in the United States, including one in Puerto Rico. Children were eligible if they were born to mothers with HIV and were 7-16 years old at study entry. Data from physical examinations, clinical histories, and medical record reviews were obtained at each semi-annual study visit. Lifetime health, including hearing health, and antiretroviral (ARV) histories were collected from prior studies or extracted through chart reviews.

DPOAE data were reported for each ear and categorized as no response (<3 dB signal-to-noise ratio [SNR]), intermediate response (3 dB - <6 dB SNR), and complete response (≥ 6 dB SNR) across the four frequency bins obtained (1, 2, 3, and 4 kHz). To measure overall cochlear function, no response within a frequency bin was assigned a score of 0, an intermediate response was assigned a 1, and a complete response was assigned a 2. This score was summed across the four frequency bins for an integer from 0 to 8 in each ear. To compare cochlear function between PHIV and PHEU participants, the DPOAE score was categorized as an ordinal variable with 3 levels, again within each ear: low cochlear function (defined as scores of 0-4); moderate cochlear function (scores of 5-7); high cochlear function (score of 8).

Demographic variables, birth characteristics, and caregiver and household characteristics were compared by HIV infection status. For PHIV participants, disease severity measures at the time of the audiometric examination were analyzed.

Proportional odds models for ordinal logistic regression were used to evaluate the association of HIV status, as well as other covariates, with the ordinal DPOAE outcome (low, moderate, or high). Multivariable models were built including HIV status and any predictors with a p-value <0.20 in univariable models. Only predictors with a p-value <0.1 were kept in the final multivariate model. Since each participant had DPOAE measures for both ears, generalized estimating equation (GEE) models were used to account for within subject correlation.

RESULTS

DPOAE data were available for 172 children overall, including 89 (52%) PHIV and 83 (48%) PHEU children from 10 of the 14 PHACS AMP sites. PHIV children (mean age=13.9 years; SD=3.1) were significantly older than PHEU children (mean age=11.4 years; SD=2.6) at the time of the examination. Among the 89 PHIV children, 72% had a HIV viral load <400 copies/mL at the examination with a median CD4% of 35. Twenty-four percent had a prior AIDS-defining condition (CDC class C) while 36% were CDC class B (symptomatic) at the time of the hearing examination. Most of the children (73%) were receiving protease inhibitor-based highly active antiretroviral therapy (HAART).

Overall, most children had high cochlear function (64.3%), while 17.3% had moderate, and 18.5% had low cochlear function. Table 1 shows the results of both univariable and multivariable ordinal logistic regression analyses. HIV infection was not associated with DPOAE scores, before and after adjustment for gender and repeated ear infections, but female participants had a trend toward higher odds of higher DPOAE scores than males (adjusted odds ratio [aOR]=1.77, 95% confidence interval [CI]:0.94-3.32, $p=0.08$). A history of repeated ear infections was marginally associated with lower odds of higher DPOAE scores (aOR=0.49, 95% CI:0.23-1.02, $p=0.06$). Among PHIV participants only, the final multivariable model indicated that having a viral load ≥ 400 copies/mL was associated with lower odds of a high DPOAE score (aOR=0.37, 95% CI: 0.14-0.96, $p=0.04$), and female participants had a trend of higher odds of higher DPOAE scores (aOR=2.29, 95% CI: 0.94, 5.59, $p=0.07$).

DISCUSSION

This is one of the first studies in which the association between HIV and cochlear function, as measured by DPOAEs, has been evaluated in children. HIV infection was not associated with poorer DPOAEs scores in this study cohort; in other words, cochlear function was similar between PHIV and PHEU children. In the present study, PHIV children with higher viral load had significantly poorer cochlear function. There are currently only data from adults in which researchers evaluated aspects of HIV disease status and DPOAEs.^{5,6} van der Westhuizen et al⁶ found no association between CDC disease classifications and DPOAEs. Torre et al⁵ found no statistically significant associations of HIV disease status (CD4+, CD8+, and current HIV viral load) or treatment components with poorer DPOAEs in HIV+ adults. All of the adults studied by Torre et al,⁵ however, were virologically controlled, possibly leading to the lack of an association.

Medications such as aminoglycosides have been shown to reduce the level of DPOAEs,⁸ but data on ototoxic effects of HIV medications on DPOAEs are lacking. An informative analysis of HIV medications on DPOAEs in the present study was not likely since 95% of the PHIV children were on ART and 73% were on an ARV regimen that consisted of HAART with protease inhibitor. Ototoxic effects on hearing have been reported in case reports of HIV-infected adults treated with nucleoside analog reverse transcriptase inhibitors (NRTIs) such as zidovudine and combinations of stavudine and lamivudine.⁹ In HIV-infected children, however, there was no association between HAART and hearing loss.^{7,10}

One limitation of the current study is that DPOAE measures were not a required procedure within the AMP hearing protocol. These measures were only obtained when site audiologists included DPOAEs as part of their study-required audiological examination. Thus, data included in this study represent a non-random sample of the PHACS AMP participants. A second limitation is that HIV-unexposed children were not included as a comparison group in this study. Lastly, DPOAE data were categorized, albeit into clinically relevant categories, but having the continuous DPOAE data would have allowed for a more thorough evaluation of cochlear function. The majority (64%) of the participants in the current study had a complete response (> 6 dB SNR) at each frequency bin.

DPOAEs only represent a portion of the auditory system responsible for hearing sensitivity (OHCs within the cochlea); therefore, some other mechanism within the auditory system may contribute to the differences in hearing sensitivity for HIV status. Perhaps the inner hair cells within the cochlea or other structures within the neural pathway are more affected by HIV infection. One measure that can evaluate the auditory neural pathway, at least to the level of the brainstem, is the auditory brainstem response (ABR) although there are no ABR data in PHIV or HEU adolescents or young adults. Further study is needed, possibly including ABRs, to determine which mechanisms in the underlying structures are contributing to the differences in hearing sensitivity among PHIV, PHEU, and HIV-unexposed children.

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Table 1

Ordinal logistic regression using generalized estimating equations for DPOAE score by child demographics and caregiver characteristics

Predictor	Unadjusted			Adjusted		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Association among all 162 participants						
HIV-infected	0.73	(0.39, 1.37)	0.33	0.78	(0.41, 1.47)	0.44
Age (years)	0.92	(0.83, 1.02)	0.12			
Female	1.84	(0.98, 3.45)	0.06	1.77	(0.94, 3.32)	0.08
Black	1.28	(0.61, 2.68)	0.52			
Hispanic	0.57	(0.29, 1.11)	0.10			
BMI z-score	0.94	(0.73, 1.20)	0.61			
Birth weight <2.5 kg	0.60	(0.29, 1.24)	0.17			
Gestational age <37 weeks	0.95	(0.45, 1.98)	0.88			
Small for gestational age	0.48	(0.16, 1.43)	0.18			
Household income <20K	0.99	(0.53, 1.85)	0.97			
Caregiver is biological parent	0.80	(0.42, 1.51)	0.49			
Caregiver married	0.90	(0.47, 1.71)	0.75			
Report of repeated ear infections	0.48	(0.23, 0.98)	0.04	0.49	(0.23, 1.02)	0.06
Association among 86 PHIV participants						
Viral load >400 copies/mL	0.46	(0.19, 1.13)	0.09	0.37	(0.14, 0.96)	0.04
CD4% <35	0.47	(0.20, 1.10)	0.08			
CDC class C	0.63	(0.23, 1.76)	0.38			
Nadir CD4% <15	1.37	(0.53, 3.56)	0.52			
Peak viral load >500K copies/mL	1.78	(0.67, 4.73)	0.25			

CI=confidence interval, BMI=body mass index, CDC=Center for Disease Control and Prevention.

Adjusted model for all participants includes female gender and repeated ear infections:

Final multivariate model for PHIV participants only includes 2 covariates: Viral load >400 copies/mL and gender (aOR=2.29 (0.94, 5.59), p=0.07).