

Middle Ear Function in Human Immunodeficiency Virus (HIV)-Infected South African Children

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Abstract

Children with human immunodeficiency virus (HIV) infection are more likely to have hearing loss and are more susceptible to middle ear infections. The purpose of this study was to quantitatively measure middle ear function, using tympanometry, in perinatally HIV-infected (PHIV) and HIV-uninfected children living in Cape Town, South Africa. Hearing-related health questionnaire data were obtained before testing. Bilateral otoscopy and tympanometry were completed in 37 PHIV and 24 HIV-uninfected children. Otoscopy was performed to evaluate debris in ear canals and to observe the tympanic membrane. Ear canal volume (Vec), peak acoustic admittance (peak Ytm), and tympanogram peak pressure (TPP) were obtained. Presence of outer and middle ear pathologies was determined. Data were compared between PHIV and HIV-uninfected children. Parent/caregiver report of past middle ear infection was higher in PHIV children (34.2%) compared with HIV-uninfected children (25.0%). Risk for reported history of middle ear infection was higher in PHIV children classified as World Health Organization (WHO) stage IV compared to other WHO stages. Outer ear otorrhea was present in two PHIV children and no HIV-uninfected children. There were no significant differences for Vec, Ytm, and TPP between PHIV and HIV-uninfected children. Tympanometry data for PHIV and HIV-uninfected children were similar, although PHIV children had a higher rate of outer ear otorrhea.

Keywords: Children, Perinatal HIV infection, Middle ear function, Otorrhea.

Introduction

Otitis media is a common pathology in children. The World Health Organization (WHO) reports the prevalence of chronic suppurative otitis media (CSOM) ranging from <1%

to 7.8% [1]. Human immunodeficiency virus-infected (HIV-infected) children who are immunocompromised are at higher risk for this opportunistic infection [2-8]. Further, greater immunosuppression in HIV-infected children is associated with both a higher rate of otitis media and greater severity of otitis media [6] and more symptomatic HIV-infected children are at higher risk for recurrent episodes of otitis media [2,5].

Additionally, recent research has shown that HIV-infected children <6 years receiving highly active antiretroviral therapy (HAART) had significantly lower prevalence of CSOM compared to those HIV-infected children ≤6 years not receiving HAART. Importantly, for HIV-infected children >6 years, there was no significant difference in the prevalence of CSOM between those receiving HAART and those not receiving HAART [8]. In most cases, CSOM is accompanied by otorrhea. In the Children with HIV Early Antiretroviral Therapy (CHER) trial, HIV-infected children who began ART early had a significantly lower risk of otorrhea compared to those on deferred ART [9]. To summarize, HIV-infected children are more at risk for various types of otitis media, with or without otorrhea, but HAART can reduce episodes of otitis media [8] along with decreased otorrhea in children on ART [9].

The prevalence and severity of otitis media in HIV-infected children has been studied; however, the evaluation of middle ear function using tympanometry is lacking. Thus, the purpose of this research was to evaluate middle ear function in perinatally HIV-infected (PHIV) and HIV-uninfected children.

Method

Participants

Children were recruited from pediatric outpatient clinics within Tygerberg Children's Hospital, Cape Town, South Africa. All children were between the ages of 4 and 14 years at the time of

testing. This age range was appropriate given the typical age of children seen at pediatric clinics and given what was required of the child as a participant.

Procedures

San Diego State University Institutional Review Board (IRB) and the Stellenbosch University Health Research Ethics Committee approved all study procedures. Written informed consent to participate in the study was obtained from the child's parent or legal guardian in the home language. Children >7 years of age provided assent.

Research assistants interviewed parent/caregivers in their home language and completed a hearing-related health questionnaire with them. Hearing-related questions included past reports of middle ear infections and parent/caregiver concerns about the child's hearing. For PHIV children, data on HIV viral load, CD4%, CD4 cell count data, and disease severity were obtained from medical records within 6 months of middle ear measures.

Audiology graduate students completed the research protocol in a clinic room designated for this study. Outer ear canals and tympanic membranes were examined using otoscopy, and middle ear function was evaluated bilaterally using tympanometry (GSI 39 Auto Tymp). Ear canal volume (Vec), peak acoustic admittance (peak Ytm) and tympanic peak pressure (TPP) were determined for each participant.

Statistical Analysis

Middle ear function was defined using Vec, peak Ytm, and TPP and was compared between PHIV and HIV-uninfected children. Risk factors for middle ear problems were evaluated by fitting logistic regression models to determine odds ratios (ORs) and corresponding 95% confidence intervals (CIs). For PHIV children only, associations between measures of middle ear function and HIV disease severity as well as HIV treatment were evaluated. Middle ear data were analyzed individually for each ear using the Wilcoxon rank-sum test. Analysis of percent of parent/caregiver report of middle ear infection was conducted using Fisher's exact test. All statistical analyses were conducted using SAS Version 9.1.2 (SAS Institute, Cary, NC).

Results

This study included the same 61 children (37 PHIV [23 females, 14 males], 24 HIV-uninfected [8 females, 16 males]) that participated in the study by Torre et al. [10]. Extensive demographic data are shown in Torre et al. [10]. Briefly, in Table 1 PHIV children were mostly female (62.2%), black race (73.0%) and spoke Xhosa (67.6%) as the primary language at home. In contrast, HIV-uninfected children were mostly male (66.7%), mixed race (58.3%) and spoke Afrikaans (58.3%) as the primary language at home. Lastly, 34.2% of parents/caregivers reported a middle ear infection in a PHIV child, and 25% reported a middle ear infection in an HIV-uninfected child. Though this difference was not statistically significant, the unadjusted risk for reported middle ear infection was higher in PHIV children (OR=1.70, 95% CI: 0.54-5.34, p=0.37). Furthermore, PHIV children classified as WHO stage IV had twice the odds of reported middle ear

infections compared to children with WHO stage II or III classification (OR=2.18, 95% CI: 0.53-9.01, p=0.28); however, this risk was not statistically significant. Since all PHIV children had HIV viral loads below the lower detectable limit (<400 or <50 copies/mL), therefore, this variable was not used in any analyses. Mean CD4% was 35.5 (SD=6.9) and mean CD4 cell count was 1301.7 cells/mm³ (SD=592.3). Four children had missing CD4% data and two children had missing CD4 cell count data. CD4% and CD4 cell count were not significant predictors of reported middle ear infections [CD4%: F(1,30)=1.18, p>0.05; CD4 cell count: F(1,30)=3.02, p>0.05].

Two of the PHIV children were identified with otorrhea and immediately referred to their physician once testing was completed. No HIV-uninfected children presented with otorrhea.

For children with flat tympanograms, peak Ytm was 0 millimhos, and this value was included in subsequent analyses. However, TPP cannot be determined for flat tympanograms, so this value was missing. Thus, six PHIV children had flat tympanograms with missing TPP data and two of these children had flat tympanograms bilaterally. Two HIV-uninfected children had a flat tympanogram and one of these HIV-uninfected children had flat tympanograms bilaterally. All children with flat tympanograms were referred to their physician for follow-up testing. Table 2 shows the means and standard deviations for the tympanogram data in each ear by HIV infection status. Although PHIV children had lower mean peak Ytm and more negative TPP, none of the differences between groups were statistically significant. In subsequent analyses of PHIV children only, WHO status, CD4%, and CD4 cell count also were not associated with poorer middle ear function.

Discussion

PHIV children in the present study had a higher rate of reported middle ear infections, more otorrhea, and more flat tympanograms compared with HIV-uninfected children. This is one of the few studies to incorporate quantitative tympanometry data to evaluate middle ear function in PHIV children. Although other researchers [3,11] have reported types of tympanograms for children, specific data were not reported. For example, Chao et al. [3] used tympanometry to evaluate middle ear pathologies in HIV-infected children, using a classification of: Type A (normal), Type B (flat), or Type C (negative middle ear pressure) and found 38.1% with flat tympanograms either unilaterally or bilaterally. This rate is higher than the rate in the current study which presented only 8 children (13.1%) with flat tympanograms. This difference is most likely a result of the health of the HIV-infected children in Chao et al. [3]. In that study, 40 (29.8%) HIV-infected children had a most recent CD4 count ≤500 cells/mm³ and 59 (44.4%) HIV-infected children had a most recent HIV viral load >400 copies/mL.

Two PHIV children in the current study had present otorrhea whereas no HIV-uninfected child presented with otorrhea. Statistics were not completed given the small numbers, though other researchers have shown that HIV-infected children in Africa have significantly more present or past episodes of otorrhea [7]

Table 1: Sex distribution and responses to specific hearing health questions stratified by infection status are shown for the 37 PHIV children and 24 HIV-uninfected children in this study

	Infection Status	
	PHIV	HIV-uninfected
Sex		
Female	23 (62.2%)	8 (33.3%)
Mean age, yrs (SD)	6.7 (1.6)	6.5 (1.6)
Male	14 (37.8%)	16 (66.7%)
Mean age, yrs (SD)	6.9 (1.6)	8.0 (1.4)
Mother/caregiver report of middle ear infection ¹ (n, % Yes)	13 (34.2%)	6 (25.0%)
Mother/caregiver suspect a hearing loss (n, % Yes)	10 (27.0%)	1 (4.1%)
Has child ever had a hearing test (n, % Yes)	14 (37.8%)	7 (29.2%)
Has child ever used hearing aids (n, % Yes)	1 (2.7%)	0 (0.0%)

¹Two mother/caregivers of a PHIV child did not report history of middle ear infection

Table 2: Means and standard deviations for ear canal volume, peak Ytm, and tympanogram peak pressure are shown. These data are further stratified by ear and HIV infection status

Audiometric Outcome	Infection Status		p-value ¹
	PHIV	HIV-uninfected	
Ear Canal Volume (Vec), in mmhos			
Left Vec Mean (SD)	0.7 (0.2)	0.8 (0.2)	0.28
Right Vec Mean (SD)	0.7 (0.2)	0.8 (0.2)	0.08
Peak Ytm, in mmhos			
Left Ytm Mean (SD)	0.5 (0.3)	0.7 (0.8)	0.57
Right Ytm Mean (SD)	0.5 (0.3)	0.7 (0.6)	0.17
Tympanogram Peak Pressure (TPP), in daPa			
Left TPP Mean (SD)	-44.8 (67.3)	-24.5 (30.1)	0.11
Right TPP Mean (SD)	-47.4 (45.7)	-31.7 (51.6)	0.22

¹Comparison between PHIV and HIV-uninfected children. mmhos-millimhos; SD-standard deviation; daPa-dekascals

and significantly more episodes of recurrent otorrhea [12].

None of the differences in the current study were statistically significant. These findings were most likely a result of PHIV children who started HAART at a relatively early age and who were virologically suppressed and immunologically competent based on mean CD4% and mean CD4 cell count. Adherence to HAART maintains virological suppression but these initial data suggest that HAART may not be ototoxic to the middle ear. Because the mean age of the children in Chao et al. [3] was just under 10 years, these children were on HAART for just over 4 years. As a result, they started treatment later than the present study cohort. The PHIV children in the current study were all on HAART, had high CD4 cell counts, and undetectable viral loads.

It should be noted that most of the PHIV children in the present study were taking a specific HAART regimen (zidovudine, lamivudine, and lopinavir/ritonavir) and were virologically controlled. This is important because younger children taking HAART had significantly lower rate of chronic otitis media

compared to those children on ART [8]. The HIV-infected children on HAART did, however, have significantly higher CD4 cell counts compared with HIV-infected children on ART. The PHIV children in the current study were all on varying HAART regimens, had high CD4 cell counts, and undetectable viral loads. Thus, no comparisons can be made using these variables.

PHIV children in this study with a WHO stage IV classification did have a higher, but not significant, risk of reported middle ear infections. Further, WHO status was not associated with any tympanometry variables. The lack of significance differences is most likely a result of small sample size. To date, this is the first study to evaluate the association between HIV disease variables and middle ear characteristics. The association between HIV disease status and hearing loss has been reported. HIV-infected children identified as a current or prior CDC class C diagnosis had significantly higher odds of hearing loss compared to those children with any other CDC classification [11].

Early identification of middle ear problems is important for all children, but especially for those who may have compromised

immune systems, such as HIV-infected children. Recurrent otitis media in younger children has been associated with phonological development delays [13] and, given that more symptomatic HIV-infected children are more likely to have recurrent episodes of otitis media [2,5], early identification and treatment is therefore necessary. Treatment of acute otitis media episodes is most often with antibiotics in an effort to eliminate the infection. When various antibiotic regimens are unsuccessful, chronic otitis media can also be treated with tympanostomy tubes. The risk here is that the use of tubes has been shown to lead to higher pure-tone thresholds [14]. The benefits of treatment should therefore be weighed against the side effects, since permanent hearing loss such as this can impact a child's speech and language development [15-17].

One limitation of this study is that the lack of statistical significance could have been a result of the small sample size. Another limitation is that only PHIV and HIV-uninfected children were included in the present study. Further testing of middle ear function is needed in children who are HIV-exposed, but uninfected (HEU). With the mother-to-child-transmission rates decreasing [18,19] due to better perinatal care for HIV-infected mothers, there will be increasing numbers of HEU children seen at clinics. Determining the effects of HIV and ART exposure on middle ear function will further contribute to the literature on perinatal HIV and overall auditory function.

Conclusion

In conclusion, by including quantitative tympanometry data, the results of this study contribute to a growing literature on the effects of HIV on middle ear function in children. PHIV children in this study had a higher risk of middle ear problems; none of the risks, however, were statistically significant. The lack of statistical significance does not preclude the need for PHIV children to be followed carefully for middle ear pathologies. Finally, this study can be seen to have significant clinical implications in the assessment and management of these groups. First, otoscopy and, at a minimum, screening tympanometry should be implemented during routine check-ups to identify middle ear problems, specifically flat tympanograms, in PHIV children. Second, starting children on early ART will result in the preservation of healthy CD4 levels, and virological control can ultimately reduce middle ear problems in PHIV children.

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