Newborn Hearing Screenings in Human Immunodeficiency Virus-Exposed Uninfected Infants

Torre P 3rd1*, Zeldow B2, Yao TJ4, Hoffman HJ5, Siberry GK6, Purswani MU7, Frederick T8, Spector SA9, and Williams PL2

1School of Speech, Language, and Hearing Sciences, San Diego State University, San Diego, CA, USA
2Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, MA
3Epidemiology and Statistics Program, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA
4Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA
5Albert Einstein College of Medicine, Department of Pediatric Infectious Disease, Bronx-Lebanon Hospital Center, Bronx, NY, USA
6Department of Maternal, Child & Adolescent Center for Infectious Diseases and Virology, University of Southern California, Alhambra, CA, USA
7Department of Pediatrics, University of California San Diego, La Jolla, CA and Rady Children’s Hospital San Diego, CA, USA

Abstract

Perinatal HIV infection and congenital cytomegalovirus (CMV) infection may increase the risk for hearing loss. We examined 1,435 infants enrolled in the Surveillance Monitoring of ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network, a prospective study of the safety of in utero antiretroviral (ARV) exposures. We determined the proportion of perinatally HIV-exposed uninfected (HEU) newborns who were referred for additional hearing testing, and evaluated the association between in utero ARV exposures and newborn hearing screening results. Using a nested case-control design, we also examined congenital CMV infection in infants with and without screening referral. Congenital CMV infection was determined based on CMV DNA detection using a nested PCR assay in peripheral blood mononuclear cells obtained within 14 days of birth. Among the 1,435 infants (70% black, 31% Hispanic, 51% male), 45 (3.1%) did not pass the hearing screen and were referred for further hearing testing. Congenital CMV was associated with lower odds of a newborn hearing screening referral [adjusted odds ratio (aOR) = 0.41, 95% confidence interval (CI): 0.14-1.00]. Exposure to Atazanavir was linked to higher odds of newborn screening referral, although not attaining significance [aOR = 1.84, 95% CI: 0.92-3.56]. Maternal ARV use may have varying effects on newborn hearing screenings. These results highlight the importance for audiologists to be knowledgeable of in utero ARV exposures in HEU children because of the possibility of higher referrals in these children.

Keywords: Newborn; Hearing; Human Immunodeficiency Virus; Cytomegalovirus, In Utero Antiretroviral Exposure

Abbreviations


Introduction

Universal newborn hearing screening in the United States was implemented following the 1993 NIH Consensus Development Conference that endorsed the screening for hearing loss of all newborns before leaving the hospital [1]. This landmark move led to an unprecedented state-by-state effort to promote mandatory newborn screening, which was bolstered by Congressional passage of the Newborn and Infant Hearing Screening and Intervention Act of 1999 that provided funding for statewide programs [2,3]. Late identification of permanent hearing loss can impair long-term speech and language development, and, subsequently, educational achievement [4,5]. The overall rate of permanent hearing loss has been reported as approximately 2 per 1000 live births [6,7]. Human immunodeficiency virus (HIV) is a risk factor for hearing loss in children and adolescents [8], but the potential link between hearing loss and in utero exposure to maternal HIV infection and HIV medications has not been well studied.

Studies of hearing screening results obtained from babies born to mothers infected with HIV are limited. Two studies have observed about two-fold higher risk of hearing loss for HIV-exposed uninfected (HEU) infants as compared to HIV-unexposed and uninfected (HUU) infants, although neither finding attained statistical significance due to the low prevalence of hearing loss [9,10]. In addition, neither accounted for congenital cytomegalovirus (CMV), which is well-known to be linked to sensorineural hearing loss [11-14] and has a higher prevalence in neonates born to mothers with HIV [15,16]. While the prevalence of congenital CMV in HEU infants has decreased with the advent of highly active antiretroviral therapy (HAART), it remains higher than in the general population [17].

Early identification of newborn hearing loss has important implications for the child’s speech, language and educational development. Since congenital CMV infection has been identified as a risk factor for permanent sensorineural hearing loss [13], screening for CMV co-infection in this group of infants is important in understanding hearing loss in HEU. The objectives of this project were to: 1) determine the proportion of HEU children referred for additional testing following a newborn hearing screening in the Surveillance Monitoring of ART Toxicities (SMARTT) cohort study (a protocol within the Pediatric HIV/AIDS Cohort Study [PHACS]); 2) evaluate the association of in utero antiretroviral (ARV) exposures with newborn hearing screening results; 3) evaluate the association between newborn hearing screening results and other risk factors and 4) examine congenital CMV infection in a subset of infants with and without further hearing referrals as a result of the newborn screening.

Materials and Methods

The study population was the Dynamic Cohort of the SMARTT study which prospectively enrolls pregnant women and their newborns from week 22 of gestation through 72 hours after birth,
and follows both the mothers and their children annually. The SMARTT study is a US based, multisite, prospective cohort study designed to evaluate the effects of in utero antiretroviral (ARV) exposure on outcomes across several domains among HEU infants (for additional details of the SMARTT study design, see Williams et al. [18]. Newborn hearing screening and follow-up screening results were collected from the medical record and then reported to the SMARTT study on study-specific data collection forms. Hearing screenings included ototacoustic emission (OAE) measures, automated auditory brainstem response (AABR) measures, or both depending on the hospital protocol. The primary outcome for this analysis was the hearing screening result (pass or refer) using OAE or AABR.

Maternal ARV data were retrospectively collected for the entire pregnancy through chart review or from prior studies; information collected included start and stop dates of each individual ARV drug so that both duration and timing of exposure (by trimester) could be characterized. The primary exposures of interest were in utero ARV exposure overall during pregnancy and within individual trimesters. HAART was considered as any regimen containing at least three drugs from at least two different drug classes. Regimens that included three nucleoside reverse transcriptase inhibitors (NRTIs) were also evaluated, as were individual drug classes (NRTI, non-NRTI, and protease inhibitors) and individual ARV agents. Demographic characteristics and maternal and infant characteristics were collected by questionnaire and medical record review and treated as possible risk factors. Substance use during pregnancy was self-reported by mothers as reported previously [19].

A nested sub-study within SMARTT was conducted to address the issue of congenital CMV, since the SMARTT study itself did not determine CMV infection status on all newborns. Congenital CMV was determined in a subset of participants based on CMV DNA detection in peripheral blood mononuclear cells (PBMCs) drawn at the entry study visit (usually at birth) and stored in the PHACS repository using a sensitive nested PCR assay [20]. Samples were chosen in a case-control design with four samples (subject to sample availability) from infants who passed the newborn hearing screen for every one infant who was referred for further testing.

Demographic differences between infants who passed and those who were referred for further hearing testing were examined using chi-square or Wilcoxon tests, as appropriate. The prevalence of hearing screening referral and its exact 95% confidence interval (CI) were calculated under a binomial distribution. Due to the relatively rare outcome of not passing a newborn hearing screening, exact logistic regression models were used to evaluate the association of maternal ARV exposures with newborn hearing outcomes. Adjusted models included a priori identified confounders with a p-value < 0.15 in unadjusted analyses (Supplemental Table 1).

### Results

As of January 1, 2013, of 1,435 SMARTT infants were enrolled and had newborn hearing screening data. The infants were primarily black (70%), with 31% Hispanic and 51% male. Among these 1,435 infants, 45 (3.1%, exact 95% CI: 2.3% - 4.2%) did not pass the newborn hearing screening and were referred for further testing. Of the 1,435 infants, 1,406 (98%) had detailed information on child demographics and maternal characteristics (Table 1) and subsequent analyses were restricted to these 1,406 infants. Almost all infants (1,382 or 98%) were exposed to either HAART or a triple NRTI regimen, with 707 (50%) exposed in the first trimester. The most common ARV exposures (Supplemental Table 2) were lamivudine (67%) and zidovudine (66%); 43% were exposed to Tenofovir; 24% to Atazanavir, and 5% to efavirenz. Only 17 infants (1%) had no recorded ARV exposure.

Based on unadjusted exact logistic regression models, first trimester exposure to Tenofovir was associated with lower odds of a newborn hearing screening referral [odds ratio (OR) = 0.41, 95% CI 0.14-1.00, p = 0.049], and first trimester exposure to emtricitabine was also associated with lower odds of a referral (OR = 0.45, 95% CI 0.15-1.07, p = 0.08), although not attaining statistical significance.

### Table 1: Child and maternal characteristics by newborn hearing screening result, among infants with complete maternal antiretroviral exposure information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 1406)</th>
<th>Newborn screening result</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pass (N = 1361)</td>
<td>Refer (N = 45)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>682 (49%)</td>
<td>663 (49%)</td>
<td>0.45</td>
</tr>
<tr>
<td>White</td>
<td>406 (30%)</td>
<td>394 (30%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hispanic</td>
<td>430 (31%)</td>
<td>416 (31%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Birth Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt; 2.5 kg</td>
<td>251 (18%)</td>
<td>244 (18%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Gestational age &lt; 37 weeks</td>
<td>272 (19%)</td>
<td>263 (19%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Mode of delivery – Cesarean</td>
<td>826 (59%)</td>
<td>799 (59%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maternal Characteristics at delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother &lt; 25 years old</td>
<td>451 (32%)</td>
<td>437 (32%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maternal viral load &gt; 1000 copies/ml</td>
<td>174 (13%)</td>
<td>169 (13%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maternal CD4 count &lt; 200 cells/mm³</td>
<td>139 (10%)</td>
<td>133 (10%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Maternal substance use during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>250 (18%)</td>
<td>246 (18%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>123 (9%)</td>
<td>117 (9%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>123 (9%)</td>
<td>118 (9%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Exposed to ototoxic medication in utero</td>
<td>228 (16%)</td>
<td>216 (16%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Twenty-nine infants did not have complete maternal ARV exposure data and are not included. All 29 of these passed the newborn screening.

*Percentages based on non-missing values. Seventy did not report race; 2 ethnicity; 11 birth weight and gestational age; 12 mode of delivery; 11 mother’s age at delivery; 28 mother’s viral load at delivery; 30 mother’s CD4 at delivery; 25 exposure to tobacco, alcohol or illicit drugs.

*Otitotoxic medications include gentamicin, neomycin, streptomycin, amphotericin, erythromycin, vancomycin, ibuprofen, indomethacin, naproxen, hydrocodone, furosemide, tobramycin, and misoprostol.

(Figure 1). After controlling for maternal use of tobacco and ototoxic medications, the association between Tenofovir and screening referral remained significant [adjusted OR (aOR) = 0.39, 95% CI 0.39-0.94, \( p = 0.03 \)] and the association between emtricitabine and screening referral remained similar (Figure 1). Exposure to Atazanavir during pregnancy was associated with higher odds of newborn screening referral (aOR = 1.84, 95% CI 0.92-3.56, \( p = 0.07 \)); in addition, a similar magnitude of association was observed for infants with third trimester exposure to Atazanavir (aOR = 1.92, 95% CI 0.94-3.76, \( p = 0.07 \); data not shown).

There were no significant associations of newborn screening results with either demographic characteristics (including sex, ethnicity, and race) or maternal and birth characteristics (including mother’s age, alcohol, tobacco, or ototoxic medication use during pregnancy, birth weight, or gestation age).

**Figure 1:** Estimated associations between maternal ARV exposures and newborn hearing screening referral (or failed screening) using exact adjusted logistic regression, separated by any exposure

(a) 1st trimester exposure

(b) Associations were adjusted for maternal use of ototoxic medications and in utero tobacco exposure.
Among the 45 infants referred after the initial newborn hearing screening, 22 had acceptable PBMC samples for CMV testing and one (4.5%) was CMV-positive. Of the 1,390 infants who passed the hearing screening, 92 were tested and 5 (5.4%) were CMV-positive. Follow-up hearing testing was not available for the six CMV positive infants.

Follow-up information on subsequent hearing tests for the 45 infants referred for further testing was evaluated through January 1, 2013. Median age at follow-up was three years with the oldest child under six years. Twelve of the 45 (27%) infants did not receive any follow-up hearing testing. Twenty-four (73%) of the remaining 33 infants with subsequent follow-up passed their hearing screenings. Another nine infants (27%) continued to have some degree of hearing problems on additional screenings or testing, including one (3%) with confirmed sensorineural hearing loss after an extensive hearing examination.

Discussion

Exposure to Atazanavir overall and specifically in the third trimester was linked with higher odds of a referral, but this association did not reach statistical significance. A recent report from within the same cohort found a significant association between exposure to Atazanavir and delayed language developmental [21]. In that analysis, the significantly higher odds increased further if the exposure to Atazanavir occurred after the first trimester. This potential relationship between perinatal exposure to Atazanavir and language delay and possibly hearing problems requires further study.

Conversely, exposure to Tenofovir in the first trimester was associated with significantly lower odds of a referral for further hearing testing. Further, first trimester exposure to emtricitabine, typically given in tablets co-formulated with Tenofovir was also associated with lower odds of a referral, but this did not attain statistical significance.

Alternative approaches for evaluating associations between exposures and binary outcomes in the setting of rare events (eg., hearing screening referral) have also been proposed, such as rare events logistic regression [22]. Utilizing rare events logistic regression (conducted using "relogit" in Stata 11), similar results were obtained to those shown in Supplemental Table 2, providing further support for the current conclusions.

Results of newborn hearing screening in HEU infants in SMARTT showed that 3.1% (45/1435) were referred for further testing, which is lower than the approximate 10% first referral rate previously reported in one statewide program in Rhode Island of all newborns [8]. This referral rate is also lower than that reported by SMARTT showed that 3.1% (45/1435) were referred for further testing. Further, first trimester exposure to emtricitabine, typically given in tablets co-formulated with Tenofovir was also associated with lower odds of a referral, but this did not attain statistical significance.

Conversely, exposure to Tenofovir in the first trimester was associated with significantly lower odds of a referral for further hearing screening, 22 had acceptable PBMC samples for CMV testing and one (4.5%) was CMV-positive. Of the 1,390 infants who passed the hearing screening, 92 were tested and 5 (5.4%) were CMV-positive. Follow-up hearing testing was not available for the six CMV positive infants.

Follow-up information on subsequent hearing tests for the 45 infants referred for further testing was evaluated through January 1, 2013. Median age at follow-up was three years with the oldest child under six years. Twelve of the 45 (27%) infants did not receive any follow-up hearing testing. Twenty-four (73%) of the remaining 33 infants with subsequent follow-up passed their hearing screenings. Another nine infants (27%) continued to have some degree of hearing problems on additional screenings or testing, including one (3%) with confirmed sensorineural hearing loss after an extensive hearing examination.

The proportion of congenital CMV infection in HEU children in the U.S. [23,24] was 5/92 = 5.4% in infants who passed the hearing screening. Another nine infants (27%) continued to have some degree of hearing problems on additional screenings or testing, including one (3%) with confirmed sensorineural hearing loss after an extensive hearing examination.

Discussion

Exposure to Atazanavir overall and specifically in the third trimester was linked with higher odds of a referral, but this association did not reach statistical significance. A recent report from within the same cohort found a significant association between exposure to Atazanavir and delayed language developmental [21]. In that analysis, the significantly higher odds increased further if the exposure to Atazanavir occurred after the first trimester. This potential relationship between perinatal exposure to Atazanavir and language delay and possibly hearing problems requires further study.

Conversely, exposure to Tenofovir in the first trimester was associated with significantly lower odds of a referral for further hearing testing. Further, first trimester exposure to emtricitabine, typically given in tablets co-formulated with Tenofovir was also associated with lower odds of a referral, but this did not attain statistical significance.

Alternative approaches for evaluating associations between exposures and binary outcomes in the setting of rare events (eg., hearing screening referral) have also been proposed, such as rare events logistic regression [22]. Utilizing rare events logistic regression (conducted using "relogit" in Stata 11), similar results were obtained to those shown in Supplemental Table 2, providing further support for the current conclusions.

Results of newborn hearing screening in HEU infants in SMARTT showed that 3.1% (45/1435) were referred for further testing, which is lower than the approximate 10% first referral rate previously reported in one statewide program in Rhode Island of all newborns [8]. This referral rate is also lower than that reported by SMARTT showed that 3.1% (45/1435) were referred for further testing. Further, first trimester exposure to emtricitabine, typically given in tablets co-formulated with Tenofovir was also associated with lower odds of a referral, but this did not attain statistical significance.

The Joint Committee on Infant Hearing [3] requires that newborns receive a hearing screening before leaving the hospital or at least by one month of age. The specific protocol for this screening is not standardized across hospitals but the universally accepted measures are OAEs and ABRRs. The recording parameters for these measures as well as the pass/referral criteria can also vary. Because of this, one limitation of this study is that newborn screening protocols did vary across sites. Although OAE and ABR measures have different sensitivity and specificity rates for identifying hearing loss, the primary objective of this study was to identify HEU children who were referred for further hearing screening. Initial hearing screening data were obtained retrospectively and across various SMARTT sites within the U.S. and Puerto Rico so it was difficult to control for the various hearing screening protocols used. Another limitation is the lack of complete follow-up hearing data when a newborn was referred, or whether or not the newborn even had follow-up services after the initial referral.

Although HIV mother-to-child-transmission rates have declined dramatically in the U.S. [24] the number of HEU children will continue to increase. The decrease in HIV mother-to-child transmission is directly related to the expanded use of HAART during pregnancy. With the increasing number of ARVs and ARV combinations available for HIV treatment, it is important for future studies to further evaluate these potential adverse effects.

Acknowledgements

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2014, in alphabetical order: Ann & Robert H. Lurie Children's Hospital of Chicago: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; Baylor College of Medicine: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris; Bronx Lebanon Hospital Center: Murli Purswani, Emma Stuart, Anna Cintron; Children's Diagnostic & Treatment Center: Ana Puga, Dia Cooley, Patricia Garvie, James Blood; New York University School of Medicine: William Borkowsky, Sandra Deygoo, Helen Rozelman; Rutgers – New Jersey Medical School: ArryDieudonne, Linda Bettica, Susan Adambata, St. Jude Children's Research Hospital: Katherine Knapp, Kim Allison, Megan Willkins; San Juan Hospital/Department of Pediatrics: Midnela Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; SUNY Downstate Medical Center: Hermann Mendez, Ava Dennie, Susan Bewley; Tulane University Health Sciences Center: Chi Dola, Robert Maupin, Karen Craig, Patricia Siros; University of Alabama, Birmingham: Marilyn Crain, Newana
Beatty, Dan Marullo; University of California, San Diego; Stephen Spector, Jean Manning, Sharon Nichols; University of Colorado Denver Health Sciences Center. Elizabeth McFarland, Jenna Wallace, Carrie Chambers, Christine Reed; University of Florida/Jacksonville; Mobeen Rathore, Kristi Stowers, Ann Usitalo; University of Illinois, Chicago; Kenneth Rich, Lourdes Richardson, Renee Smith; University of Miami; Gwendolyn Scott, Claudia Flores, Elizabeth Willen; University of Southern California; Toni Frederick, Mariam Davtyan, Maribel Mejia; University of Puerto Rico Medical Center; Zoe Rodriguez, Ibet Heyer, Nydia Scally-Trifilio.

Note: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

References


*Corresponding author: Peter Torre 3rd, School of Speech, Language, and Hearing Sciences, San Diego State University, San Diego, CA 92182-1518, USA. Tel: 619-594-4787, Fax: 619-594-7109; E-mail: ptorre@mail.sdsu.edu.

Received Date: May 07, 2016, Accepted Date: August 22, 2016, Published Date: September 5, 2016.

Copyright: © 2016 Torre P 3rd, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.