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Total serum bilirubin levels and sensorineural hearing loss in the US adolescents: NHANES 2007–2010

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ABSTRACT

Objective: We aimed to investigate whether current levels of total serum bilirubin are associated with different subtypes of sensorineural hearing loss (SNHL) in adolescents.

Methods: A set of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) (2007–2010) was used. A subset of 1404 adolescents was sampled for measurements of total serum bilirubin, tympanometry, and average pure tone threshold at low-frequencies (LPTA: 500, 1000, 2000 Hz) or high-frequencies (HPTA: 3000, 4000, 6000, and 8000 Hz). SNHL was defined as the hearing loss that had type A tympanograms with a peak admittance of 0.3 ml or greater. Associations between serum bilirubin (square-root transformed) and different subtypes of SNHL were evaluated using binary or multinomial logistic regression models with 4-year sampling weights. The bootstrap method was used for estimation of variance and 10-fold cross-validation for assessment of overfitting issue.

Results: Total serum bilirubin levels were found to be associated with any high-frequency (HPTA > 15 dB in at least one ear, adjusted odds-ratio (OR_a)(bootstrap 95% confidence interval) = 3.29(1.31–8.19), p = 0.011), but not with any low-frequency (LPTA > 15 dB in at least one ear), SNHL in the US adolescents. Furthermore, high-frequency SNHL with HPTA > 15 dB in both ears (bilateral) or HPTA ≥ 25 dB in at least one ear, compared to that with HPTA > 15 dB in one ear only (unilateral) or HPTA = 15–25 dB in at least one ear, had a stronger association with total serum bilirubin levels (OR_a = 5.37(1.27–22.65), p = 0.022 for bilateral; OR_a = 2.64(0.84–8.25), p = 0.094 for unilateral; OR_a = 5.00(0.95–26.58), p = 0.058 for HPTA ≥ 25 dB in at least one ear; as well as OR_a = 3.06(1.15–8.25), p = 0.025 for HPTA = 15–25 dB in at least one ear). No severe overfitting problems were found.

Conclusion: Our findings suggest that current levels of total serum bilirubin may be informative in predicting and/or targeting high-frequency SNHL in the US adolescents.

1. Introduction

The prevalence of hearing loss in US adolescents increased significantly from 14.9% in 1988–1994 to 19.5% in 2005–2006 [1]. Slight hearing loss (> 15–24 dB) in young children can impair speech and language development and lead to decreased educational achievement and impaired social-emotional development [2–4]. Sensorineural hearing loss (SNHL) is a multifaceted condition. Common risk factors of SNHL in children may include genetics, infection, and exposure to loud noise [5].

Bilirubin is a catabolic product of heme that presents in heme proteins such as hemoglobin, myoglobin, catalase, and cytochrome P450 enzymes, etc. [6,7]. A reference range of total serum bilirubin including conjugated (direct) and unconjugated (indirect) in adults at the Massachusetts General Hospital in the US was 0.3–1.0 mg/dL [8]. Many conditions or disorders may cause hyperbilirubinemia in adolescents, such as hemolytic anemias, Gilbert syndrome, viral infections, liver diseases, and hepatotoxic medications [9]. Recent studies have shown that neonatal hyperbilirubinemia is associated with the risk of SNHL in children who aged less than 8 years [10,11]. However, no studies on the relationship of current serum bilirubin levels with SNHL, particularly with various clinical subtypes of (e.g., low- or high-frequency, bilateral or unilateral, and slight or mild or more severe) SNHL in adolescents have been found.

Thus, in the present study, we aimed to investigate whether current total serum bilirubin levels are associated with different subtypes of SNHL in the US adolescents by using a set of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES)

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(2007–2010). The obtained results may aid in the development of a biomarker for precisely predicting and/or of an intervention target for reducing the risk of various subtypes of SNHL in adolescents.

2. Materials and methods

2.1. Study population and sampling

About 2577 adolescents aged 12–19 years from two cycles of the NHANES data (2007–2010) were included. We excluded the participants who had no compliance & pressure measures (n = 206), compliance < 0.3 & pressure < −150 or > 100 (n = 308), and pure tone audiometry (PTA) < 0 or no PTA assay (e.g., valued as '888' or '.') (n = 482) in either left or right ear, as well as no total serum bilirubin assay (n = 169), or a diagnosis of diabetes (n = 8). The remaining 1404 participants were included in the final analysis. Four-year weights were calculated and applied to reduce selection biases arising from nonresponse and differential probabilities of selection among race, ethnicity, income, gender, and age based on the NHANES Estimation Procedures (2007–2010) [12] and Analytic Guidelines (1999–2010) [13].

2.2. Measurement of outcomes – audiometry

Based on the NHANES Audiometry Procedures Manual [14], the NHANES 2007–2010 Audiometry Examination was composed of 1) an audiometric questionnaire to identify conditions affecting audiometric testing or result interpretation; 2) a brief otoscopic screening exam of ear canals and eardrums to identify abnormalities or conditions that require alternate audiometric procedures or medical referral and influence result interpretation; 3) tympanometry to measure middle ear volume, pressure, compliance, and gradient for identifying middle ear pathologies that might contribute to hearing loss; and 4) pure tone air conduction audiometry to measure the participants' hearing thresholds at frequencies across the range of human hearing (500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz). All Audiometry Components were conducted in a dedicated, sound-isolating room in the mobile examination center (MEC) [14].

For the tympanometry, an 84-point tympanogram for each ear was recorded by an automated tympanometer. The equivalent volume (compliance) data for pressure values range from −300 daPa to +198 daPa, and thus, the responses for a particular ear were contained in a series of 84 equally-spaced sequential measurement variables and each successive variable represents a 6 daPa increase in applied pressure. These tympanometry raw data were used to create tympanometric graphs of compliance as a function of pressure for each ear by using a SAS™ program provided in Appendix A of the Audiometry – Tympanometry doc file online (https://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/AUXTYM_F.htm). Tympanogram type was used as supplemental evidence for identifying a hearing loss as conductive or sensorineural [15]. SNHL was defined as the hearing loss that had type A tympanograms with a peak admittance of 0.3 ml or greater, whereas, type A tympanograms were those with peak admittance occurring between +100 and −150 daPa [15].

For pure tone air conduction audiometry, the air conduction pure tone thresholds at 0.5, 1, and 2 kHz were averaged and designated as the low-frequency pure tone threshold average (LPTA) while those at 3, 4, 6, and 8 kHz were averaged and designated as the high-frequency PTA (HPTA) [1].

We used slight hearing loss (PTA > 15 dB) [1] as a cut-off to define three pairs of outcome variables, i.e., any low-/high-frequency SNHL (LPTA or HPTA > 15 dB in at least one ear) (designated as LSNHL & HSNHL, respectively); any low-/high-frequency unilateral or bilateral SNHL (LPTA or HPTA ≤15 dB in both ears, > 15 dB in one ear only, or > 15 dB in both ears) (designated as LSNHL_UB & HSNHL_UB, respectively); and multiple levels of low-/high-frequency SNHL (LPTA or HPTA ≤15 dB, 15–25 dB, or ≥25 dB in at least one ear) (designated as LSNHL_M & HSNHL_M, respectively).

2.3. Measurement of exposure variable –total serum bilirubin

Based on the NHANES Laboratory Procedures Manual [16], total bilirubin concentration (mg/dL) in serum or plasma was measured using a timed-endpoint Diazo method, a colorimetric analysis at 520 nm, in which the analytical range was 0.1–30.0 mg/dL and the sensitivity was 0.1 mg/dL.

2.4. Potential covariates

Demographic variables including gender, age, race, education, and the ratio of family income to poverty were derived from demographics questionnaires in the home by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system. For the participants who were 16–19 years of age, a direct interview was conducted whereas for those who were under 16 years, a proxy provided relevant information regarding the survey participants [17,18].

Smoking status including active and passive (i.e., environmental tobacco smoke exposure) smoking was determined using the level of serum cotinine, a major metabolite of nicotine and having a substantially longer half-life in plasma (15–20 h) compared to nicotine (0.5–3 h) [19]. Serum cotinine was measured by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry [16]. Smoking status was defined as "yes" when serum cotinine concentration ≥10 ng/ml [20,21].

Three consecutive blood pressure (BP) readings were obtained after resting quietly in a sitting position for 5 min. If a blood pressure measurement was interrupted or incomplete, a fourth attempt was made. All BP determinations (systolic and diastolic) were taken in the mobile examination center (MEC) [22]. Three good BP readings were averaged and subsequently used for prehypertension definition. Prehypertension was defined as a blood pressure measurement of 120/80 mmHg or greater regardless of whether it is less than the 90th percentile [23].

Variables ear infection history and exposure to loud noise or music in last 24 h were derived from the audiometry questionnaire (AUQ) section of the NHANES Sample Person Interview Questionnaire [24].

2.5. Data management and statistical analysis

All outcome variables (LSNHL & HSNHL, LSNHL_UB & HSNHL_UB, LSNHL_M & HSNHL_M) were categorical and expressed as number and weighted percentage (Table 1). Exposure (total serum bilirubin concentration) was treated as a continuous variable with a weighted median and quartiles 1 & 3 due to a skewed distribution. The distribution of total serum bilirubin concentration was skewed towards lower values; therefore, we performed square-root transformation to normalize the distribution before the regression analysis. In order to simplify the analysis of the relationship between outcomes and exposure, all covariates were categorized as binary and were presented as weighted percentages (Table 1). A chi-square test was used to examine whether a discrete outcome variable was associated with the individual potential confounding variable. For continuous exposure variable, its weighted median with a 95% confidence interval (CI) was used to determine whether the association between exposure and individual dichotomized confounding variable was statistically significant.

In regression modeling, for the binary outcome variable (LSNHL and HSNHL), a classical logistic regression model was used; and for the multinomial outcome variables (LSNHL_UB and HSNHL_UB, LSNHL_M and HSNHL_M), a multinomial logistic regression model was applied. A process of model selection was conducted to generate a final model for each outcome variable. A 10-fold cross-validation procedure [25] was used to evaluate overfitting issue for each final model. Specifically, the

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