Research Article

The Relationship Between Iron Deficiency Anemia and Sensorineural Hearing Loss in the Pediatric and Adolescent Population

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Purpose: A correlation between iron deficiency anemia (IDA) and sudden sensorineural hearing loss (SNHL) was described in adults. In this study, we examined if there is a relationship between IDA and hearing loss in the pediatric population.

Method: This was a retrospective cohort study of data collected from the Informatics for Integrating Biology and the Bedside database from 2011 to 2016. Children and adolescents 4–21 years old seen at Penn State Milton S. Hershey Medical Center, Hershey, PA, were examined for hearing loss and IDA status. Hearing loss was determined by International Classification of Disease-9 and -10 codes, and IDA was determined by both low hemoglobin and serum ferritin levels for age and sex.

Results: We identified 20,113 patients. Prevalence of hearing loss and IDA was 1.7% and 2.3%, respectively. The prevalence of all hearing loss was 3.0% in the IDA cohort and 1.7% in those without IDA. Children and adolescents with IDA are at increased odds of developing SNHL (adjusted odds ratio: 3.67, 95% CI [1.60–7.30]).

Conclusions: Children with IDA demonstrate increased likelihood of SNHL. Although correction of IDA in those with hearing loss has yet to be linked to improvements in hearing outcomes, screening for and correcting IDA among pediatric patients will positively affect overall health status.

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Hearing loss encompasses both a partial or complete loss of hearing. This may be further classified into conductive (CHL) or sensorineural (SNHL). CHL occurs when sound waves are inefficiently conducted through the outer ear to the ear drum and middle ear ossicles, usually resulting in the inability to hear faint sounds. This may occur due to maladies, such as, but not limited to, otitis media, perforated eardrum, and malformation of the outer or middle ear. CHL can commonly be treated either by medical or surgical options (Gifford, Holmes, & Bernstein, 2009). On the contrary, SNHL is

characterized by damage to the inner ear or cochlea, resulting in the inability to either appropriately transduce the vibrations of the ossicles to neural impulses or transmit these neural impulses from the ear, down the vestibulocochlear nerve to the brainstem. SNHL is usually a permanent form of hearing loss as the result of ototoxic medications, hereditary hearing loss, or trauma/illness (Gifford et al., 2009). On occasion, SNHL may have a rapid onset, usually unilaterally, called sudden SNHL. Prognosis is based on many factors, including age, duration of hearing loss, and pattern of hearing loss; however, in cases of idiopathic sudden SNHL in which no treatment was sought, around 45%–65% of patients are estimated to regain some hearing thresholds with those percentages increasing to around 90% with early physician intervention (Kuhn, Heman-Ackah, Shaikh, & Roehm, 2011).

Iron deficiency anemia (IDA) is a subset of anemia in which patients usually exhibit low hemoglobin, serum ferritin, serum iron, and/or increased soluble transferrin receptor. It can usually be easily treated with oral iron supplementation. Premature infants, infants fed exclusively breast milk or formula lacking iron fortification, children with reduced dietary intake or poor dietary absorption, and those with significant blood loss are at the highest risk for developing IDA (American Academy of Pediatrics, 2009). Neurotransmitter metabolism, DNA synthesis, and DNA

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repair mechanisms all depend on iron as a cofactor. Specific to the pediatric population, iron is involved in the central and peripheral nervous systems (nerve myelination, dendritic arborization) with downstream effects on development, learning, and long-term memory (Badaracco, Ortiz, Soto, Connor, & Pasquini, 2008; Beard, 2003; Chenoufi et al., 1997; Espinosa de los Monteros et al., 1999; Fretham, Carlson, & Georgieff, 2011; Jorgenson, Sun, O'Connor, & Georgieff, 2005; Jorgenson, Wobken, & Georgieff, 2003; Radlowski & Johnson, 2013; Todorich, Zhang, & Connor, 2011; Yu, Steinkirchner, Rao, & Larkin, 1986; Zhang, 2014). Iron also plays a role in the vascular system. It is a key component of hemoglobin, the protein within red blood cells responsible for carrying oxygen to body tissues. The prevalence of IDA in the United States is estimated at 2%–3% for toddlers up to age 3 and increasing to 5% for adolescent girls with significant variation by sex, socioeconomic status, body mass index, and race (Brotanek, Gosz, Weitzman, & Flores, 2007, 2008; Looker, Dallman, Carroll, Gunter, & Johnson, 1997; Pfeiffer et al., 2013).

S. D. Chung, Chen, Lin, and Hung (2014) reported on the relationship of IDA with sudden SNHL among adults in a large case-control study from Taiwan. It was hypothesized that the inner ear blood supply, which is highly susceptible to ischemic damage, was further compromised by IDA, leading to sudden SNHL. The role of iron in both the vasculature and nervous system raises the possibility of its relationship with common types of pediatric hearing loss. As the epidemiology of hearing loss varies by age, sudden SNHL is less common in the pediatric population (J. H. Chung, Cho, Jeong, Park, & Lee, 2015). Some studies have linked SNHL to sickle cell anemia in pediatrics (Alabi et al., 2008; Koussi et al., 2001; Mgbor & Emodi, 2004; Odetoyinbo & Adekile, 1987; Saito et al., 2011; Samperi, Bertuna, Rossi, Poli, & Serra, 2005; Taipale, Pelkonen, Bernardino, Peltola, & Pitkaranta, 2012) with the proposed mechanism of this relationship being the occlusion of the blood vessels by the sickled red cells, resulting in ischemia (Ondzotto et al., 2002). However, this mechanism would not be applicable to individuals with IDA because sickle cell anemia patients have normal levels of iron, and the sickle cell shape is only characteristic of those with sickle cell anemia. Despite the relationship between sickle cell anemia and hearing loss, limited information is available specific to how IDA may influence risk of hearing loss in children older than infancy.

Although, to date, there has been a significant amount of research studying the effects of IDA and cognitive development in children (reviewed in Nyaradi, Li, Hickling, Foster, & Oddy, 2013), there is very limited human data suggesting a relationship between IDA and hearing loss in the pediatric population. Iron-deficient rat models (including young rats) have demonstrated altered histopathology of the inner ear, including strial atrophy and reduction of spiral ganglion cells, resulting in development of SNHL (Sun et al., 1992, 1987). In addition, data have shown that Chilean infants with IDA have altered myelination and increased auditory brainstem responses at age 4 relative to those without IDA as an infant (Algarin, Peirano, Garrido,

Pizarro, & Lozoff, 2003), suggesting that iron deficiency may play a critical role in the auditory developmental period during childhood. Therefore, the objective of this study was to examine the relationship between IDA and SNHL, CHL, and presence of any hearing loss among a cohort of pediatric and adolescent patients 4–21 years old. The hypothesis was that IDA would have a stronger relationship with SNHL compared with CHL in the pediatric population. Identifying a relationship between IDA and hearing loss may facilitate earlier diagnosis of hearing loss, improve screening guidelines, and better the understanding of iron status on neurological and vascular function.

Method

Study Population

This study was a retrospective cohort study using data obtained from deidentified electronic medical records within the National Institutes of Health–supported Informatics for Integrating Biology and the Bedside (i2b2) database (Murphy et al., 2010). This database includes medical records from all patients seen at the Penn State Milton S. Hershey Medical Center in Hershey, PA, from 2011 until the present. It is updated monthly to include new patients. The database currently includes more than 750,000 unique patients. This study was determined to be exempt by the Pennsylvania State University College of Medicine Institutional Review Board.

Queries were performed using patient encounters from January 1, 2011, to January 31, 2016. Individuals with IDA were identified by at least one event consistent with both low ferritin and low hemoglobin laboratory values determined by age and sex. Published criteria for low ferritin vary between < 10 ng/mL and < 15 ng/mL. As few patients had ferritin levels drawn and even fewer had levels below 10–12 ng/mL, the decision was made to define low ferritin as < 15 ng/mL for this analysis (Centers for Disease Control, 1998; Looker et al., 1997; World Health Organization, 2011). Low hemoglobin values were designated as follows: boys and girls ages 4–5 years old < 11.2 g/dL, boys and girls ages 6–11 years old < 11.8 g/dL, boys ages 12–15 years old < 12.6 g/dL, boys/men ages 16–19 years old < 13.6 g/dL, men ages 20–21 years old < 13.7 g/dL, girls ages 12–15 years old < 11.9 g/dL, and girls/women ages 16–21 years old < 12.0 g/dL (Looker et al., 1997).

Hearing loss was defined by the International Classification of Disease (ICD)-9 and ICD-10 codes: CHL 389.00–389.08, H90.0, H90.11–H90.12, and H90.2; SNHL 389.10–389.18, H90.3, H90.41–H90.42, and H90.5; and all hearing loss 389.0–389.9 and H90.0–H90.8. Hearing loss–related ICD codes may have been added by a primary care provider, otolaryngologist, or audiologist following a visit with a hearing-related complaint. Formal audiogram testing would not be required. Queries were stratified by age and sex. The cohort excluded those with sickle cell disease (282.6 and D57) due to previous studies linking sickle cell anemia with hearing loss (Alabi et al., 2008; Koussi et al.,

2001; Mgbor & Emodi, 2004; Odetoyinbo & Adekile, 1987; Saito et al., 2011; Samperi et al., 2005; Taipale et al., 2012).

Patients with IDA and hearing loss had at least one event consistent with both low ferritin and low hemoglobin as well as at least one diagnosis code for the hearing loss of interest. A temporal analysis was performed to confirm that hearing loss was diagnosed within 2 years after the patient was considered to have IDA.

A population without both IDA and hearing loss was selected from i2b2 by excluding patients with any of the aforementioned hearing loss–related ICD-9 or ICD-10 codes and IDA. These cohorts had either normal hemoglobin or normal ferritin or demonstrated normal values for both laboratory tests on the basis of age and sex. In a similar manner, populations with hearing loss and no IDA (hearing loss only) and with IDA and without hearing loss (IDA only) were selected.

The presence of potential confounding variables for IDA and hearing loss, including race (Brotanek et al., 2007; Lin et al., 2012), weight status (Cepeda-Lopez, Aeberli, & Zimmermann, 2010; Kim et al., 2016), and nutritional status (Aspuru, Villa, Bermejo, Herrero, & López, 2011; Emmett & West, 2015) was also evaluated. Because body mass index or growth percentiles are not available in i2b2, ICD-9 and ICD-10 codes for overweight and obesity (278.00–278.03 and E66.0–E66.9) were used to determine the prevalence of this comorbidity in our populations. Nutritional deficiency was accounted for using the entire spectrum of ICD-9 and ICD-10 codes as follows: nutritional deficiency (260–269.99), malnutrition (E40–46), and other nutritional deficiencies (E50–64). These codes account for all vitamin deficiencies, nutritional deficiencies, and malnutrition disorders.

Statistical Analysis

Patient demographics were analyzed comparing individuals with and without IDA by two-tailed chi-squared test using a 2×2 contingency table with the reference group for each category. Prevalence of hearing loss was determined via counts from i2b2. A two-tailed chi-squared test by 2×2 contingency table was performed to compare the prevalence of hearing loss in those with and without IDA. Both univariate and multivariate conditional logistic regression were performed to measure the risk of developing hearing loss with IDA. Categorical variables were converted into binary (or quaternary for race) terms. Using the *glm* model in R software, univariate logistic regression was initially performed followed by multivariate logistic regression adjusted for variables found at $> 1\%$ prevalence in both cohorts that were significantly different between those with and without IDA (age, sex, race, protein-calorie malnutrition, and vitamin D deficiency). An odds ratio with 95% confidence intervals (CIs) were obtained for each variable. Sensitivity analysis was performed to account for underestimated IDA prevalence using values recalculated at $X + 3\%$ for male participants or $X + 5\%$ for female participants. All statistics were performed using R software (The R Project for Statistical Computing, Vienna, Austria).

Results

Demographics

Among 20,113 individuals 4–21 years of age with serum ferritin and hemoglobin values available, the prevalence of IDA was 2.3%. Consistent with published data, the IDA prevalence was greatest among adolescent female individuals 12–21 years (3.3%). The average hemoglobin was significantly lower in the IDA group compared with those without IDA (10.6 ± 1.8 g/dL and 13.7 ± 1.4 g/dL, respectively, $p < .0001$). In a similar manner, average serum ferritin was also significantly lower in the IDA group compared with the no IDA group (8.9 ± 3.6 ng/mL and 54.3 ± 210.0 ng/mL, respectively, $p < .0001$). The prevalence of IDA was not significantly different between overweight and obese children and adolescents compared with those of normal weight. In contrast, the prevalence of IDA was significantly different on the basis of age, sex, race, and nutritional status—to be specific, the presence of nutritional marasmus, protein-calorie malnutrition, and vitamin D deficiency (see Table 1).

Bivariate Analysis of Hearing Loss and IDA

The relationship between SNHL and IDA was significant among children ages 4–11 years ($p = .0001$) and among the entire cohort ages 4–21 years ($p = .0016$). The presence of all hearing loss was also significant among the entire cohort ($p = .0376$). A relationship was not described between IDA and CHL (see Table 2). To account for potential underrepresentation of IDA with the usage of lab values to distinguish groups, a sensitivity analysis was performed. This analysis used a 3% IDA prevalence for male participants and 5% for female participants. The relationship between children and adolescents ages 4–11 years old ($p < .0001$) and 4–21 years old ($p < .0001$) with IDA and SNHL remained significant. The sensitivity analysis also revealed a significant relationship between boys ages 4–11 years old ($p = .0096$) and male participants 4–21 years old ($p = .0051$) and SNHL (see Supplemental Material S1).

Odds of Hearing Loss Among Those With IDA

Logistic regression confirmed increased odds of all hearing loss among those with IDA (adjusted odds ratio [OR]: 1.79, 95% CI [0.99–2.99]). To be specific, increased odds of SNHL were found with an adjusted OR: 3.67 (95% CI [1.60–7.30]). Male sex reduced odds of hearing loss, and protein-calorie malnutrition and vitamin D deficiency increased odds (see Table 3). Multivariate analyses were adjusted for age, sex, race, protein-calorie malnutrition, and vitamin D deficiency. Although we initially only included variables that were present in $> 1\%$ of both IDA and no IDA cohorts in our regression model, the data remained significant after including nutritional marasmus.

Table 1. Demographics (*n* = 20,113).

Characteristics	Total participants	No iron deficiency anemia participants (%)	Iron deficiency anemia participants (%)	<i>p</i> value
Total ages 4–21	20,113	19,649 (97.7)	464 (2.3)	
Ages				
4–11	6,978	6,849 (98.2)	129 (1.8)	.0019
12–21	13,135	12,800 (97.4)	335 (2.6)	reference
Sex				
M	9,343	9,176 (98.2)	167 (1.8)	< .0001
F	10,770	10,473 (97.2)	297 (2.8)	reference
Race				
Asian	295	282 (95.6)	13 (4.4)	.0017
Black or African American	1,241	1,191 (96.0)	50 (4.0)	< .0001
Other	84	82 (97.6)	2 (2.4)	.7336
Unknown	2,497	2,398 (96.0)	99 (4.0)	< .0001
White	15,996	15,696 (98.1)	300 (1.9)	reference
Weight (ICD-9/ICD-10)				
Overweight (278.02, E66.3)	639	627 (98.1)	12 (1.9)	.4723
Obesity (278.00, 278.01, 278.03, E66.01, E66.09, E66.8, E66.9)	1,042	1,016 (97.5)	26 (2.5)	.7011
Normal weight	18,432	18,006 (97.7)	426 (2.3)	reference
Nutritional deficiency diagnoses (ICD-9/ ICD-10)				
Ascorbic acid deficiency (267)	3	2 (66.7)	1 (33.3)	.1069
B-complex deficiency (266.2)	19	17 (89.5)	2 (10.5)	.1187
Mineral deficiency (269.3)	2	0 (0)	2 (100)	
Nutritional marasmus (261)	17	12 (70.6)	5 (29.4)	< .0001
Other nutritional deficiency (269.8, E61.8)	5	3 (60.0)	2 (40.0)	< .0001
Protein-calorie malnutrition (262, 263.9, E43, E44.0, E44.1, E46)	424	390 (92.0)	34 (8.0)	< .0001
Vitamin A deficiency (264.9)	2	0 (0)	2 (100)	
Vitamin D deficiency (268.9, E55.9)	259	228 (88.0)	31 (12.0)	< .0001
Vitamin K deficiency (E56.1)	1	0 (0)	1 (100)	
No nutritional deficiencies	19,750	19,309 (97.8)	441 (2.2)	reference

Note. Analysis performed by two-tailed chi-squared test. Bolded values are those that are significant (*p* < .05). ICD = International Classification of Disease.

Discussion

The study results demonstrate increased odds of SNHL among children and adolescents 4–21 years old with IDA. The relationship with SNHL rather than CHL is likely due to the pathophysiology of SNHL and the impact of IDA on the vasculature and the nervous system of the inner ear, making it more susceptible to SNHL. The blood supply to the cochlea relies solely on the labyrinthine artery, resulting in an area that is highly susceptible to ischemic damage. Individuals with IDA are at greater risk for ischemic stroke due to lower hemoglobin levels and impaired oxygen-carrying capacity (Chang et al., 2013; Dubyk et al., 2012). However, the pediatric population is not at high risk for ischemia, so other potential mechanisms of this association should be explored. Animal studies have shown that iron deficiency alone can influence cochlear changes, including stria atrophy and reduction of spiral ganglion cells, as well as increasing peroxidative damage to the inner ear cells through altering succinic dehydrogenase and peroxidase activity (Sun, Li, Xiao, Li, & Wang, 1990; Sun et al., 1987). Iron deficiency alters myelin production by causing degradation of lipid saturase and desaturase and impairing energy production (Todorich, Pasquini, Garcia, Paez, & Connor, 2009).

Iron therapy has been described to reverse pulmonary vascular remodeling in an iron-deficient rat model (Cotroneo et al., 2015) and IDA-induced peripheral neuropathy in children (Kabakus et al., 2002), suggesting there may be a benefit to iron therapy as a treatment for hearing loss. Increased auditory brainstem response latencies were described in infants diagnosed with IDA, suggesting that IDA during infancy may have prolonged effects on the auditory system even after correction of IDA (Algarin et al., 2003; Yehuda & Yehuda, 2006). Although correction of IDA in those with hearing loss has yet to be linked to improvements in hearing outcomes, these study results raise issues related to screening for IDA in a preventive care context and routine evaluation for children and adolescents diagnosed with SNHL.

When a survey of pediatric otolaryngologists attempted to establish a consensus on workup of SNHL in children and adolescents, no “standard” workup emerged. However, computed tomography scans, genetic testing, and electrocardiograms were ordered with greater frequency than routine laboratory studies, such as complete blood count (Rutherford, Lerer, Schoem, & Valdez, 2011). The study results did not clarify if the complete blood count was done primarily for evaluation of infection versus anemia. Therefore, including hemoglobin screening (as part of the

Table 2. Prevalence of hearing loss among those with and without iron deficiency anemia (IDA).^a

Age (years)	Conductive hearing loss			Sensorineural hearing loss			All hearing loss (mixed, conductive, sensorineural)		
	IDA (%)	No IDA (%)	p value	IDA (%)	No IDA (%)	p value	IDA (%)	No IDA (%)	p value
4–11									
M	1/84 (1.2)	51/3,919 (1.3)	.9301	2/84 (2.4)	32/3,919 (0.8)	.1281	2/84 (2.4)	126/3,919 (3.2)	.6759
F	1/45 (2.2)	32/2,930 (1.1)	.4798	3/45 (6.7)	20/2,930 (0.7)	< .0001	5/45 (11.1)	83/2,930 (2.8)	.0024
All	2/129 (1.6)	83/6,849 (1.2)	.732	5/129 (3.9)	52/6,849 (0.8)	.0001	7/129 (5.4)	209/6,849 (3.1)	.1390
12–21									
M	1/83 (1.2)	20/5,257 (0.4)	.2375	1/83 (1.2)	29/5,257 (0.6)	.4336	2/83 (2.4)	74/5,257 (1.4)	.4531
F	2/252 (0.8)	35/7,543 (0.5)	.4567	2/252 (0.8)	31/7,543 (0.4)	.3603	5/252 (2.0)	53/7,543 (0.7)	.0216
All	3/335 (0.9)	55/12,800 (0.4)	.2073	3/335 (0.9)	60/12,800 (0.5)	.2676	7/335 (2.1)	127/12,800 (1.0)	.0520
4–21									
M	2/167 (1.2)	71/9,176 (0.8)	.5416	3/167 (1.8)	61/9,176 (0.7)	.0826	4/167 (2.4)	200/9,176 (2.2)	.8535
F	3/297 (1.0)	67/10,473 (0.6)	.4373	5/297 (1.7)	51/10,473 (0.5)	.0052	10/297 (3.4)	136/10,473 (1.3)	.0030
All	5/464 (1.1)	138/19,649 (0.7)	.3459	8/464 (1.7)	112/19,649 (0.6)	.0016	14/464 (3.0)	336/19,649 (1.7)	.0376

Note. Analysis performed by two-tailed chi-squared test.

^aIron deficiency anemia defined by serum ferritin < 15 ng/mL and hemoglobin on the basis of age and gender: boys and girls ages 4–5 years old < 11.2 g/dL, boys and girls ages 6–11 years old < 11.8 g/dL, boys ages 12–15 years old < 12.6 g/dL, boys/men ages 16–19 years old < 13.6 g/dL, men ages 20–21 years old < 13.7 g/dL, girls ages 12–15 years old < 11.9 g/dL, and girls/women ages 16–21 years old < 12.0 g/dL.

complete blood count) in the routine evaluation of pediatric hearing loss could be a cost-effective addition with considerable diagnostic utility.

Bright Futures, which sets the standards for pediatric preventive care, currently recommends a newborn hearing screen prior to hospital discharge. Following the birth hearing screen, children are recommended to have objective testing for hearing loss at ages 4–6, 8, and 10 years during routine preventive care visits. IDA screening is conducted at 9–12 months and then as needed for adolescents identified as high risk by interview or questionnaire (Hagan, Shaw, & Duncan, 2008). This analysis suggests for children and adolescents diagnosed with hearing loss, specifically SNHL, additional screening for IDA may be a worthwhile consideration. Hemoglobin screening is often done via point-of-care testing in the office setting. IDA is easily treated with several months of oral iron supplementation. Thus, screening and treatment would be part of currently established procedures. Although the link between correcting IDA and improving hearing health is not established,

it is known that both IDA and hearing loss have negative effects related to attention and scholastic performance, which are improved with treatment (Abbas & Valli, 2012; Bener, Kamal, Bener, & Bhugra, 2014; Cortese, Angriman, Lecendreux, & Konofal, 2012; Halterman, Kaczorowski, Aligne, Auinger, & Szilagyi, 2001; Konofal, Lecendreux, Arnulf, & Mouren, 2004; Lahat et al., 2011; Millichap, Yee, & Davidson, 2006; Schieffer, Peters, Richter, Loc, & Pawelczyk, 2015).

This analysis has allowed the use of clinical data to test the relationship between IDA and hearing loss on a large scale although certain limitations should be considered in the interpretation of the results. In i2b2, ICD-9 and ICD-10 codes are obtained through the institution's billing system. This relies on manual data entry and may be prone to error and variability in clinical interpretation for ICD codes. Only diagnoses that were billed through the medical center are captured in i2b2. Due to the deidentified nature of i2b2, the only data available from the medical record are what is captured by i2b2, thus limiting the data available

Table 3. Logistic regression to assess the association between iron deficiency anemia (IDA)^a and hearing loss.

Characteristic	Sensorineural hearing loss	Conductive hearing loss	All hearing loss
IDA ^b	3.67 (1.60–7.30)	1.74 (0.60–3.94)	1.79 (0.99–2.99)
Age	1.02 (1.00–1.04)	1.02 (1.00–1.04)	1.02 (1.00–1.04)
Race (White)	1.99 (1.64–2.40)	1.98 (1.63–2.39)	1.97 (1.63–2.37)
Sex (boys)	0.59 (0.49–0.71)	0.59 (0.49–0.72)	0.58 (0.48–0.70)
Protein-calorie malnutrition	2.64 (1.71–3.92)	2.58 (1.66–3.84)	2.64 (1.72–3.90)
Vitamin D deficiency	5.16 (3.42–7.55)	5.14 (3.41–7.51)	5.07 (3.36–7.41)

^aDefined by serum ferritin < 15 ng/mL and hemoglobin on the basis of age and sex: boys and girls ages 4–5 years old < 11.2 g/dL, boys and girls ages 6–11 years old < 11.8 g/dL, boys ages 12–15 years old < 12.6 g/dL, boys/men ages 16–19 years old < 13.6 g/dL, men ages 20–21 years old < 13.7 g/dL, girls ages 12–15 years old < 11.9 g/dL, and girls/women ages 16–21 years old < 12.0 g/dL. ^bMultivariate logistic regression analysis was adjusted for age, sex, race, protein-calorie malnutrition, and vitamin D deficiency.

on family history, newborn audiology screening, and other potential confounding variables. We are unable to accurately address the use of ototoxic medications. The commonly prescribed ototoxic medications include chemotherapeutics, such as aminoglycosides, platinum compounds, and macrolides; loop diuretics (i.e., furosemide); quinine; and nonsteroidal anti-inflammatory drugs (Schellack & Naude, 2014). A review of our patients with IDA and hearing loss demonstrate that three were on furosemide prior to the first ICD code diagnosis of hearing loss. However, dosage, flow rate, and other variables that may contribute to the ototoxicity of furosemide are unable to be captured without examining the medical records, and therefore, we did not adjust for it in our regression model. In addition, the presence of comorbidities, such as cytomegalovirus infection (Cohen, Durstenfeld, & Roehm, 2014) and meningitis (Richardson, Reid, Tarlow, & Rudd, 1997), may result in hearing loss. None of our cases were clinically diagnosed with either of these conditions.

The prevalence of IDA may have been underestimated by this study, which required values for both hemoglobin and serum ferritin to define IDA. To improve the specificity of the analysis, only individuals with at least one laboratory value (serum ferritin or hemoglobin) that was not consistent with IDA were considered without IDA. Serum ferritin and hemoglobin normally are not routinely tested in the clinic, which suggests that the patients included in our cohort without IDA had an underlying medical comorbidity that was unable to be accounted for in this analysis. In clinical practice, patients with a low hemoglobin are often presumptively treated with iron, and a serum ferritin level is not always requested (Centers for Disease Control, 1998; World Health Organization, 2011). Although the data would be compelling if the relationship between IDA and hearing loss was demonstrated for both sexes, our results did not find this when stratified according to sex. This likely is a result of our stringent criteria, reducing the power of our analysis. The total population of pediatric patients included in the database are not presented in this data set because we required laboratory values to define IDA. If no laboratory values were available, the patients were excluded, thus limiting the population available for analysis and reducing overall statistical power. However, this is not felt to be affecting the results because when we performed a sensitivity analysis to account for a potential underrepresentation of IDA in our population, the data found a significant relationship between IDA and SNHL for boys ages 4–11 years old and male patients 4–21 years old, suggesting that the original analysis demonstrated reduced power to address this association in the male sex.

The prevalence of SNHL and CHL were lower than what has been reported in the literature (Lin, Niparko, & Ferrucci, 2011; Niskar et al., 1998). However, some of the difference is likely due to the criteria used to define hearing loss in different studies. Lin et al. (2011) used National Health and Nutritional Examination Survey (NHANES) 2001–2008 data and reported a prevalence of 2.3% (95% CI [1.5–3.1%]) of bilateral and unilateral hearing loss > 25 dB among 12- to

19-year-olds, which is similar to the prevalence of 1.7% reported in this analysis (Lin et al., 2011). Other studies using NHANES data report a much higher prevalence of hearing loss in the pediatric population (Niskar et al., 1998). The NHANES data are derived from objective audiogram measurements, which differ from the clinical criteria utilized by the i2b2 database to identify cohorts. The different prevalence rates are likely due to variations in diagnostic criteria, and to our knowledge, there are no published objective criteria for comparison.

Conclusions

This study suggests a relationship between IDA and SNHL in children and adolescents. Considering screening for IDA for 4- to 21-year-olds diagnosed with SNHL would be a reasonable addition to current practice. Although treatment of underlying IDA will improve the overall health of affected children and adolescents, next steps will need to establish if this treatment specifically results in improvements to hearing health.

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