Diphtheria and Hearing Loss

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SYNOPSIS

Objective. To determine if infectious diseases usually experienced in childhood have an effect on hearing ability later in life.

Methods. The Epidemiology of Hearing Loss Study (N = 3,753) is a population-based study of age-related hearing loss in adults aged 48 to 92 years in Beaver Dam, Wisconsin. As part of this study, infectious disease history was obtained and hearing was tested using pure-tone audiometry. Hearing loss was defined as a pure-tone average of thresholds at 500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz greater than 25 decibels hearing level in either ear.

Results. After adjusting for confounders, only a history of diphtheria (n = 37) was associated with hearing loss (odds ratio [OR] 2.79; 95% confidence interval [CI] 1.05, 7.36). There was no relationship between hearing loss and history of chickenpox, measles, mumps, pertussis, polio, rheumatic fever, rubella, or scarlet fever. Only two participants with a history of diphtheria and hearing loss reported having a hearing loss before age 20.

Conclusions. Diphtheria in childhood may have consequences for hearing that do not become apparent until later in life. A possible biological mechanism for a diphtheria effect on hearing ability exists: The toxin produced by the Corynebacterium diphtheriae bacteria can cause damage to cranial nerves and therefore may affect the auditory neural pathway. These data may have important implications for areas facing a resurgence of diphtheria cases.

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INTRODUCTION

It has been widely reported that some infectious diseases can cause acute hearing loss. In the National Census of Deaf Persons study in 1971, 22.8% of the reported causes of deafness were from infectious diseases (measles, meningitis, scarlet fever, and pertussis) and an additional 13.2% were classified as caused by "other illness."[1,2] There are many mechanisms by which infectious diseases are able to cause acute hearing loss. Histopathology of the temporal bones of individuals with hearing loss associated with either measles or mumps has shown degeneration of the organ of Corti and the stria vascularis. The mechanism for such damage is suggested to be an inflammatory process that begins after invasion by the virus.[3,4] Damage to the ear can also occur from bacterial infections, such as pertussis, that may lead to complications of otitis media or mastoiditis.[5,6] Inner ear bacterial infections can develop as well, especially in the case of meningitis, which has frequently been associated with acute hearing loss.[7,8] Toxins produced by the bacteria that cause typhoid fever and diphtheria were also implicated as causes of acute hearing loss in one reference.[9] In the case of varicella-zoster virus, reactivation of the virus that caused chickenpox as a child can lead to herpes zoster oticus (Ramsay Hunt syndrome) which may acutely affect the hearing ability as an adult.[10,11]

Whereas infectious diseases have long been associated with acute hearing loss, we are unaware of any published studies that have examined the association of various childhood infectious diseases with hearing loss detected later in life. If infectious diseases can acutely affect the ear and hearing ability by so many different mechanisms, it is possible they may also have the ability to cause damage to the ear that would predispose a person to a hearing loss with age or that could cause a subtle or gradual hearing loss that might go undetected for many years. This would mean that some age-related hearing loss may have roots in infectious diseases that were experienced many years previously.

It is not unheard of for infectious diseases to cause latent sequelae that manifest many years after the initial infection has resolved. For example, progressive postpoliomyelitis muscle atrophy syndrome can occur decades after resolution of the initial infection with polio and, unlike varicella-zoster virus, is not believed to be the re-activation of the virus but a consequence of the initial damage done by the disease.[12]

More than 40% of the older adult population suffers from age-related hearing loss, also called *presbycusis,* and the etiology of this condition is not well known.[13] The Epidemiology of Hearing Loss Study (EHLS), a population-based study of older adults, was established to determine the prevalence, characteristics and causes of age-related hearing loss. Because most of the EHLS population was born before vaccines and antibiotics were widely available, it provides a unique opportunity to assess the relationship between infectious disease history and hearing sensitivity later in life.

METHODS

The EHLS is a population-based study of age-related hearing loss in adults aged 48 to 92 years from Beaver Dam, Wisconsin. Data used in these analyses were obtained at the baseline hearing examination done in 1993, 1994, and 1995. Of the 4,541 people in Beaver Dam determined to be eligible to participate, 3,753 (82.6%) participated; 3,571 of the participants completed the exam, and 182 completed the interview portion only. Of the remaining 788 eligible to participate, four (0.1%) were lost to follow-up, 180 (4.0%) died before they could be examined, and 604 (13.3%) refused to participate. The methods used to determine the eligible population of Beaver Dam are published elsewhere.[14]

Informed consent was obtained from each participant of the study population prior to examination. A detailed questionnaire administered by trained interviewers included questions about self-perception of ear and hearing problems, physician-diagnosed ear and hearing problems, and occupational and leisure noise exposures. Participants were asked if they had ever had any of the following diseases: chickenpox, diphtheria, encephalitis, measles, meningitis, mumps, pertussis, polio, rheumatic fever, rubella, and scarlet fever. Additional health and demographic information used in these analyses were collected during the five-year follow-up examination of the Beaver Dam Eye Study, a concurrent study of age-related ocular disorders in the same population-based cohort.[14]

Hearing was measured by highly trained technicians using pure-tone air- and bone-conduction audiometry.[13,15] Otoscopy and tympanometric measures also were obtained; the methods are described elsewhere.[16] Hearing thresholds were measured at 0.25 kHz, 0.5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz for air conduction. Bone-conduction thresholds were measured at 0.5 kHz and 4 kHz. Hearing loss was defined as a pure-tone average (PTA) of thresholds at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz greater than 25 decibel (dB) hearing level in either ear. A conductive

hearing loss was defined as an air-bone gap of at least 15dB at either 0.5 kHz or 4 kHz.

Analyses were done with SAS statistical software.[17] Logistic regression was used to assess the odds of hearing loss associated with a history of infectious disease. The following confounders that have previously been associated with hearing loss were controlled for during the analyses: age, gender, a history of cardiovascular disease, less than a high school education, occupational noise exposure, and smoking history. Participants were considered to have a history of cardiovascular disease if they reported that a doctor had told them they had had a stroke, myocardial infarction, or angina. Smoking history was defined as "current smoker," "past smoker," or "never smoked," where current or past smokers had to have smoked at least 100 cigarettes during their life. Occupational noise exposure was defined as ever having had a full-time job in an environment where it was necessary to speak in a raised voice or louder to be heard within two feet of another person. Furthermore, farmers with a history of driving a tractor without a cab and participants with a history of military service that included exposure to loud engines, equipment, or weapons, were considered to have a positive history of occupational noise exposure.

RESULTS

Table 1 shows the self-reported infectious disease history for the EHLS population. Participants were less likely to report "don't know" for those diseases that generally have a more severe course, such as polio, diphtheria, scarlet fever, and rheumatic fever. As expected for this cohort, measles, mumps, and chickenpox had been experienced by most of the participants. Meningitis and encephalitis were reported by less than 1% of the population (results not shown), and because it was not possible to determine the causative agents of these diseases, no further analyses were attempted.

Table 2 shows the unadjusted and adjusted odds ratios and confidence intervals for the infectious diseases and hearing loss. Only a history of diphtheria had a significant association (odds ratio [OR] 2.79; 95% confidence interval [CI] 1.05, 7.36) with hearing loss after adjusting for age, gender, education, occupational noise exposure, smoking history, and cardiovascular disease history. Further analyses of the relationship between diphtheria and hearing loss were done to control for other possible confounders. A history of target shooting, head injury, ear infections, and alcohol use were all independent predictors of hearing loss but did not significantly affect the relationship between hearing loss and diphtheria and were not retained in the final model.

Participant characteristics by history of diphtheria are shown in Table 3. Participants who reported a history of diphtheria were older than those who did not report such a history. Also, only two (5.4%) participants with a history of diphtheria reported that their hearing loss occurred before age 20, and only one of them reported that the hearing loss had occurred suddenly. The association between diphtheria and hearing loss remained (adjusted OR 2.47; 95% CI 0.96, 6.36) after those participants who reported that their hearing loss began before age 20 were excluded from the analysis. When those with a conductive or mixed hearing loss were excluded from the analysis, an adjusted OR 2.36 (95%; CI 0.89, 6.26) was found for diphtheria and sensorineural hearing loss. Participants with only a conductive hearing loss ($n = 22$) also showed a positive association with diphtheria, but the confidence intervals were large (results not shown).

To assess the validity of the self-reported history of

Table 1. Self-reported infectious disease history

	Yes		*No*		*Don't know*	
Disease	n	*Percent*	n	*Percent*	n	*Percent*
Chicken pox	2,717	76.1	532	14.9	322	9.0
Diphtheria	37	1.0	3,497	97.9	37	1.0
Measles	3,168	88.7	186	5.2	217	6.1
Mumps	2,528	70.8	747	20.9	296	8.3
Pertussis	992	27.8	2,262	63.3	317	8.9
Polio	45	1.3	3,499	98.0	26	0.7
Rheumatic fever	144	4.0	3,357	94.0	70	2.0
Rubella	1,210	33.9	1,189	33.3	1,172	32.8
Scarlet fever	468	13.1	2,968	83.1	135	3.8

Table 2. Odds ratios for infectious disease history and hearing loss

				Age and sex adjusted		*Adjusted* [a]	
Disease		n	*Percent with hearing loss*	*OR*	*95% CI*	*OR*	*95%CI*
Chicken pox							
	Yes	2,711	41.9	0.77	0.61, 0.97	0.83	0.65, 1.04
	No	529	59.2				
Diphtheria							
	Yes	37	83.8	2.95	1.12, 7.74	2.79	1.05, 7.36
	No	3,485	45.2				
Measles							
	Yes	3,158	44.4	0.72	0.50, 1.03	0.74	0.50, 1.07
	No	185	57.8				
Mumps							
	Yes	2,521	44.2	0.89	0.73, 1.08	0.88	0.72, 1.08
	No	743	48.7				
Pertussis							
	Yes	989	47.5	1.01	0.85, 1.22	1.02	0.85, 1.23
	No	2,252	43.7				
Polio							
	Yes	45	35.6	0.72	0.35, 1.47	0.67	0.32, 1.42
	No	3,485	46.0				
Rheumatic fever							
	Yes	142	43.0	0.94	0.62, 1.41	0.90	0.59, 1.36
	No	3,347	45.8				
Rubella							
	Yes	1,208	39.1	0.81	0.66, 0.98	0.83	0.68, 1.01
	No	1,186	51.3				
Scarlet fever							
	Yes	468	55.6	1.12	0.88, 1.41	1.16	0.91, 1.47
	No	2,955	44.2				

[a]Adjusted for: age, sex, occupational noise exposure, history of cardiovascular disease, smoking, and education level

OR = odds ratio

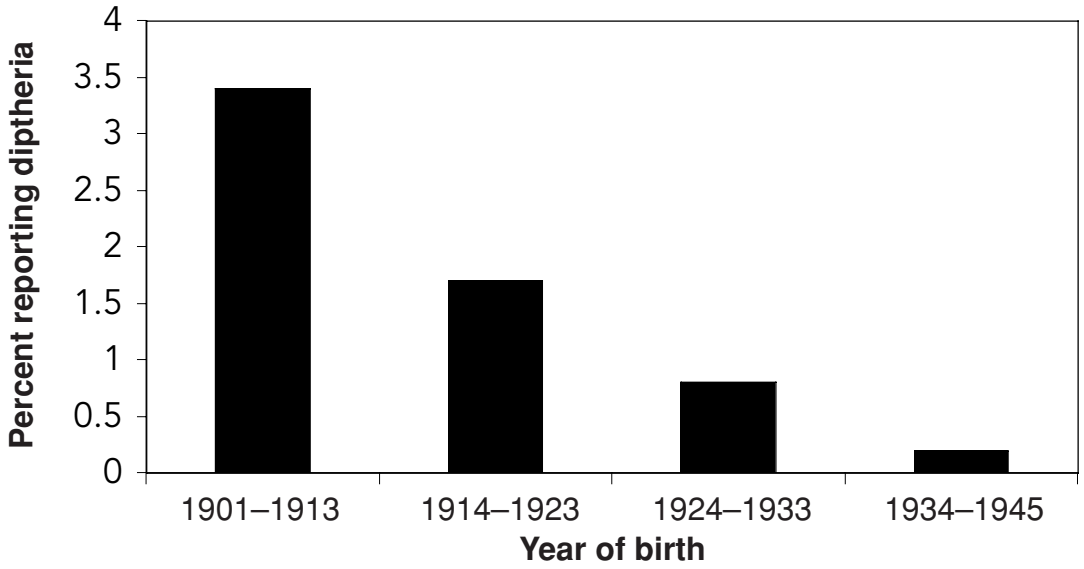
CI = confidence interval

Table 3. Characteristics of participants in the Epidemiology of Hearing Loss Study (EHLS) by history of diphtheria

Characteristic	*Diphtheria*	*No diphtheria*	*p-values*
N	37	3497	—
Mean age	75.4	65.4	<0.001
n (%) Male	16 (43.2)	1,501 (42.9)	0.97
n (%) Hearing loss	31 (83.8)	1,576 (45.2)	<0.001
n (%) Reporting a hearing loss before age 20	2 (5.7)	75 (2.3)	0.19
n (%) Sensorineural hearing loss only [a]	28 (82.4)	1,282 (40.9)	<0.001

[a]Excludes participants with a conductive hearing loss or mixed hearing loss.

Figure 1. Percent of the Epidemiology of Hearing Loss Study (EHLS) participants reporting a history of diphtheria by year of birth



diphtheria, the percentage of the EHLS population reporting diphtheria was graphed by year of birth (Figure 1). The highest percentage of reported diphtheria (3.4%) in this population was among the participants born between 1901 and 1913 (current age 80–92 years). With each 10-year decrease in age, the percentage of reported diphtheria cases decreased. Less than 0.2% of the participants in the 48 to 59-year age group and no one under age 55 reported a history of diphtheria. This is consistent with the history of diphtheria in the United States, where the number of reported cases peaked in the early 1900s and then declined.[18]

DISCUSSION

The results of this study suggest a possible association between a history of diphtheria and a hearing loss that is not detected until later in life. Infectious diseases that have been linked with acute hearing loss, such as measles, mumps, pertussis, and scarlet fever showed no significant association with hearing loss in this study. With the exception of two participants, all respondents who were aware they had a hearing loss and reported a history of diphtheria indicated that the hearing loss had begun after they reached the age of 40. If this is a true association, it implies that a history of diphtheria may predispose a person to develop a hearing loss later in life or that diphtheria may cause a mild acute loss that is not detected right away. An extensive literature search yielded only one reference to acute hearing loss as a possible consequence of diphtheria, although otitis media was also reported to be a complication of the disease.[5,9,19]

There are biologically plausible theories of ways in which diphtheria could cause hearing loss. First, neuritis may cause damage to the eighth cranial nerve, which is responsible for hearing. The toxin produced by the *Corynebacterium diphtheriae* bacteria, when absorbed by the body, can cause damage to organs far from the site of the infection and is especially associated with myocarditis and cranial and peripheral neuritis.[20] Symptoms and evidence of peripheral neuritis do not surface until 10 days to three months after the onset of the disease.[20] The delayed onset of symptoms of neuritis may be a model for damage to the nerves in the ear, which may occur slowly over time and therefore may not be recognized or attributed to the disease.

Second, cranial neuropathies caused by the toxin can lead to ciliary paralysis, which could mean that the hair cells in the cochlea are vulnerable to these effects.[20] An initial insult to the hair cells could predispose a person to a hearing loss later in life as additional insults to hair cells from such factors as loud noise or ototoxic drugs occur. The variation in the type and severity of hearing loss could also be dependent on the severity of the disease, which would vary by individual and by the strain of diphtheria experienced.

It was surprising to find that infectious diseases

previously associated with acute hearing loss showed no significant association with hearing loss in this study. Any association between measles and mumps and hearing loss may have been masked by the high rate of infection reported and the high prevalence of hearing loss in this population. Misclassification of disease history is also a possibility, because it was based on participant recall of events that occurred many years earlier. The disease rates that were reported, however, are consistent with or lower than the expected rates for an unvaccinated population during the first half of the 20th century. If the diseases are underreported, these results would be biased toward the null, or no effect. It is also possible that some participants may have had subclinical cases of disease and therefore were unaware of their true disease history.

Diphtheria has been previously associated with acute hearing loss but not with presbycusis, and this may suggest that our results are a chance finding in the study population. Because the data used for this study were cross-sectional, a temporal or causal relationship cannot be established. Knowledge of the severity of the disease, treatment of the disease, and the age at which the disease was contracted are not known. Factors that may have predisposed a participant to contracting diphtheria, such as poor living conditions or poor nutrition as a child, could also have had an effect on hearing ability.

CONCLUSIONS

At present, diphtheria is a rare disease in the United States, with only 41 respiratory cases reported between 1980 and 1994.[21] Furthermore, diphtheria has not previously been associated with presbycusis and is only briefly mentioned as a possible cause of acute hearing loss. In countries where immunization rates for diphtheria are high, the importance of these results would be primarily for those adults who were born before the widespread use of the toxoid vaccine. Russia and other former republics of the Soviet Union experienced an upsurge of diphtheria cases in the 1990s, however, so these results may have more relevance for those populations.[22] It is possible that the results of this study are a chance occurrence in this population. But if the results of this study are valid, they have interesting implications. First is the possibility that a small percentage of age-related hearing loss may not be an inevitable part of aging but the result of an infectious disease contracted many years previously. Second, because diphtheria is a vaccine-preventable disease, this would mean that a small percentage of hearing loss could be prevented in adults in the future. Finally, these results would contribute previously unknown information about the natural history of diphtheria.

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