Is Age-Related Maculopathy Related to Hearing Loss?

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Objective: To describe the relationship of age-related maculopathy (ARM) to hearing loss.

Design: Population-based cohort study.

Participants: All 3397 adults (age range, 48-92 years) living in Beaver Dam, Wis, who were examined for age-related eye disease and hearing loss from March 1, 1993, to July 18, 1995, and who had analyzable hearing thresholds in at least 1 ear and fundus photographs gradable for ARM in at least 1 eye.

Methods: Characteristics of drusen and other lesions typical of ARM were determined by grading stereoscopic color fundus photographs using the Wisconsin Age-Related Maculopathy Grading System. We used standard protocols of pure-tone air-conduction audiometry to assess hearing loss, which was defined as the pure-tone average of hearing thresholds at 500, 1000, 2000, and 4000 Hz greater than 25-dB hearing level.

Results: The prevalence of ARM was 25.4% and of hearing loss was 45.0% in this population. Both conditions were present in 15.1%. The relationships between early ARM lesions and hearing loss were not statistically significant. After controlling for age and sex, persons with late ARM were more likely (odds ratio, 3.15; 95% confidence interval, 1.34-7.42) to have hearing loss than persons without late ARM. This relation did not change when other factors related to ARM or hearing loss (eg, cigarette smoking status, history of occupational noise exposure, and history of cardiovascular disease) were entered into multivariate models.

Conclusions: These population-based estimates document the frequent coexistence of signs of ARM and hearing loss. As late ARM is an important cause of loss of vision, and as hearing loss is associated with difficulty in communicating, the high frequencies of sensory comorbidity may affect maintenance of independent functioning as people age. Further study is necessary to examine why late ARM and hearing loss are associated.

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RETINAL DISEASE and hearing loss may occur together as a result of a number of inherited genetic conditions (eg, Usher and Alport syndromes)[1-6] and delayed expression of intrauterine environmental exposures (eg, rubella and varicella).[4,7,8] In a group of 10 patients with various causes of macular degeneration (Best disease [n=1], Stargardt disease [n=3], Behr disease [n=4], and early and late age-related maculopathy [ARM] [n=2]), Singh et al[9] found 3 patients with hearing impairment, whereas none were found in a control group of 10 patients without macular degeneration. To our knowledge, there are no data available from population-based studies regarding a possible association of ARM and hearing loss in older individuals.

The underlying pathogenesis of ARM and hearing loss are poorly understood.[10,11] If ARM and age-related hearing loss are associated, the development of both may be a result of common exposures (eg, oxidative stress, cigarette smoking, and atherosclerosis).[12-14] Our purpose is to examine the relation of signs of ARM to hearing loss in a large, well-characterized, population-based study of adults ranging from 48 to 92 years of age.

RESULTS

Characteristics of the study population and the frequencies of ARM lesions (soft indistinct drusen, moderate-sized or larger drusen, increased retinal pigment, RPE depigmentation, pigmentary abnormalities, geographic atrophy, exudative degeneration, early and late ARM severity,

PARTICIPANTS AND METHODS

POPULATION

Details of the methods of identification and description of the study population have appeared in previous reports.[13-15] In summary, a private census of the population of Beaver Dam, Wis, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were 43 to 84 years of age. Of the 5924 eligible individuals, 4926 participated in the baseline examination of the Beaver Dam Eye Study (BDES) from March 1, 1988, to September 14, 1990. Ninety-nine percent of the population was non-Hispanic and white. Nonparticipants consisted of 226 persons (3.8%) who had died before the examination, 18 (0.3%) who could not be located, 337 (5.7%) who permitted an interview only (of these, 61 had moved), and 417 (7.0%) who refused to participate (of these, 39 had moved). Results of comparisons between participants and nonparticipants at the time of the baseline examination have appeared elsewhere.[15]

Before the start of the 5-year follow-up eye examination in the BDES (BDES II) on March 1, 1993, 385 (7.8%) of the participants had died. Of the 4541 surviving participants in the baseline examination, 3684 (81.1%) participated in the follow-up examination from March 1, 1993, to June 14, 1995. Four participants could not be located, 259 (5.7%) permitted an interview only (of these, 48 had moved), 423 (9.3%) refused to participate (of these, 44 had moved), and 171 (3.8%) died during the examination period. The mean and median times between the baseline and 5-year follow-up eye examinations were 4.8 years each (SD, 0.4 years).

Comparisons between participants and nonparticipants at follow-up have been presented elsewhere.[16] Persons who were alive and did not participate in the follow-up eye examination (n=686) were older at baseline than those who did (mean age, 62.7 vs 60.4 years; $P<.001$). After adjusting for age, nonparticipants who were alive during the study were more likely to have fewer years of education, a lower income, poorer visual acuity, a history of cardiovascular disease, never used alcohol, smoked more, higher serum cholesterol levels, and higher systolic and diastolic blood pressure and more likely to be retired at baseline than participatants. After adjusting for age and sex, participants were more likely to have ARM at baseline (Cochran-Mantel-Haenszel test for general association, $P=.003$).

The Epidemiology of Hearing Loss Study (EHLS) is a population-based study of hearing loss in those same Beaver Dam residents, ranging from 48 to 92 years of age, who participated in the BDES I[16] or who were seen at the baseline examination of the BDES and were alive on March 1, 1993. There were 3571 participants who underwent a hearing examination and 182 who only completed an interview. There were 3397 participants with analyzable data for this report (examined in the BDES II and EHLS and who had gradable fundus photographs from the BDES II).

A systematic sample (every 10th participant was picked, for 35 eyes from 25 participants) of fundus photographs from 266 persons with maculopathy and a history of rubella were examined for signs of rubella retinopathy. None were found. To assess the effect of non–age-related hearing loss on our results, 252 participants with the following conditions were excluded from preliminary analyses: onset of hearing loss before 30 years of age, based on self-report; history of ear surgery; or unilateral hearing loss. These exclusions had no impact on the results. Accordingly, data from all 3397 analyzable participants are reported.

MEASUREMENTS

Similar procedures were used at the baseline and follow-up eye examinations and have been described in detail elsewhere.[14,15] Informed consent was obtained from each participant at the beginning of the examination. A standardized questionnaire was administered by the examiners. Pertinent parts of the interview included a history of cigarette smoking and cardiovascular disease. Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye were examined.[17] For purposes of this report, participants in the EHLS with at least 1 eye free of confounding lesions at the follow-up eye examination (right eye, n=3301; left eye, n=3327; both eyes, n=3231) are included in the analyses.

Grading for ARM was performed in a masked fashion using a standardized protocol, the Wisconsin Age-Related Maculopathy Grading System.[18,19] This system permits the assessment of the presence and severity of 14 lesions associated with ARM. More detailed descriptions of these lesions appear elsewhere.[18-20] In brief, size and type of retinal drusen, percent of the area of the macula covered with drusen, drusen confluence, retinal pigment epithelium (RPE) depigmentation, and increased retinal pigment were determined. Pigmentary abnormality was defined as the presence of RPE depigmentation or increased retinal pigment in the macular area. For purposes of analyses, RPE depigmentation, increased retinal pigment, and pigmentary abnormality were divided into the following 2 categories: none or questionable, and present.

In the absence of signs of late ARM as defined later in article, early ARM was defined as the presence in the macular area of soft indistinct or reticular drusen or hard distinct or soft drusen plus pigmentary abnormalities. Late ARM was defined as the presence of signs of exudative age-related macular degeneration or pure geographic atrophy. Exudative macular degeneration was defined as the presence of an RPE detachment or serous detachment of the sensory retina, intraretinal or subretinal pigment epithelial hemorrhage, and/or subretinal fibrous scars. Pure geographic atrophy was defined as the presence of geographic atrophy and the absence of exudative macular degeneration. For purposes of analyses, the following 2 categories were used: absent or questionable, and present.

When both eyes of a participant were discrepant in the presence or severity of a lesion, the grade assigned for the participant was that of the worse or more severely involved eye. For example, in assigning the presence of RPE depigmentation, if RPE depigmentation was present in 1 eye only, the participant was considered to have RPE

Continued on next page

depigmentation. When drusen or signs of ARM could not be graded in 1 eye, the participant was assigned a score equivalent to that in the other eye.

The EHLS examination included a questionnaire that was administered as an interview about medical and family history, history of noise exposure, and quality of life. The hearing examination included an otoscopic evaluation,[21] screening tympanometry using commercially available equipment (GSI 37 Autotymp, Lucas GSI, Inc, Littleton, Mass),[21,22] and pure-tone air- and bone-conduction audiometry. Audiometric testing was conducted according to the recommended guidelines of the American Speech-Language-Hearing Association[23] in sound-treated booths (Industrial Acoustics Co, New York, NY), using computer-based clinical audiometers (Virtual 320, Virtual Corp, Seattle, Wash) equipped with Telephonics Dynamic Headset-50 earphones (Telephonics Corp, Farmingdale, NY). Insert earphones (E-A-RTone 3A, Cabot Safety Corp, Indianapolis, Ind) and masking were used as necessary. Pure-tone air-conduction thresholds were obtained for each ear at 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz. Bone-conduction thresholds were measured only at 500 and 4000 Hz because of time constraints. People unable to travel to the clinic site (nursing home residents, home-bound participants, and people living in remote areas [n=132]) underwent testing at their residences using a portable audiometer (Beltone 112, Beltone Electronic Corp, Chicago, Ill).

All audiometers were initially calibrated in accordance with the American National Standards Institute[24] and were periodically recalibrated during the study. Ambient noise levels were measured at each home or nursing home visit and were routinely monitored at the clinic site at the Beaver Dam Community Hospital to ensure that testing conditions complied with the American National Standards Institute.[25]

Hearing loss was defined as the pure-tone average (PTA) of thresholds at 500, 1000, 2000, and 4000 Hz greater than 25-dB hearing level.

DEFINITIONS

Current age was defined as the age at the time of the EHLS examination. Participants had a positive history of cardiovascular disease if they responded affirmatively to the questions regarding history of angina, heart attack, or stroke. Cigarette-smoking status at the time of the examination was determined as follows: Subjects were classified as having never smoked if they had smoked fewer than 100 cigarettes in their lifetime, as ex-smokers if they had smoked at least this number of cigarettes in their lifetime but had stopped smoking before the examination, and as current smokers if they had not stopped.

STATISTICAL ANALYSES

Statistical analyses were performed using version 6.09 of the SAS System.[26] Analytical techniques included contingency table analysis and logistic regression.[27] For modeling purposes, hearing loss was considered the outcome of interest, and ARM was considered the risk factor. Analyses were run for the worse eye and worse ear. Specific tests included the χ^2 test for overall association to assess unadjusted association between ARM and hearing loss, overall and within age groups; Mantel-Haenszel test for overall trend in hearing loss prevalence for variables with more than 2 discrete categories[28] (eg, none, early, late); *t* tests for differences in mean age by participation status; McNemar test for right vs left eye differences in ARM lesions and right vs left ear differences in prevalence of hearing loss; binomial tests in place of McNemar test for geographic atrophy and exudative ARM, where numbers were small; and Cochran-Mantel-Haenszel test for association for age-adjusted sex differences in prevalence of hearing loss.

and hearing loss) are presented in **Table 1** and the following tabulation:

Characteristic	No. (%) of Population
Sex	
Female	1910 (56.2)
Male	1487 (43.8)
Age, y	
48-59	1213 (35.7)
60-69	1020 (30.0)
70-79	851 (25.1)
80-92	313 (9.2)
Cigarette-smoking history	
Never	1552 (45.8)
Past	1342 (39.6)
Current	497 (14.7)
History of cardiovascular disease	
No	2897 (85.7)
Yes	484 (14.3)
History of occupational exposure to noise	
No	2344 (69.0)
Yes	1053 (31.0)

Some of the subgroups do not total 3397 due to missing data. There were no statistically significant differences in the frequency of any of the ARM lesions between right and left eyes. The prevalence of hearing loss was higher in the left ear than in the right ear in men (52.0% vs 46.9%; $P<.001$) but not in women (29.9% vs 28.9%; $P=.16$). After adjusting for age, men had a higher prevalence of hearing loss than women (59.9% vs 33.2% in the worse ear; $P<.001$).

Hearing loss and ARM were jointly present in 15.1% of the population. Hearing loss and ARM were found in 39.5% of the population 75 years of age or older. The presence of hearing loss was frequent in persons whose eyes had ARM lesions (**Table 2**). Approximately 89% of those with late ARM had hearing loss present compared with approximately 40% in people without any ARM present ($P<.001$).

Most participants (73.1%) with late ARM in the right eye had hearing loss in the right ear. The concordance on the left side was even higher (86.4%). Most participants (69.8%) with hearing loss had bilateral loss, and 40.4% with late ARM had bilateral late ARM. There was no apparent concordance between the side of the hearing loss and late ARM when late ARM was present in 1 eye only. Only 2 of the 16 participants with late ARM in the right eye only had hearing loss only in the right ear, and only 1 of the 17 participants with late ARM in the left eye only had hearing loss only in the left ear.

Table 1. Prevalence of Age-Related Maculopathy and Hearing Loss in the Study Population

Lesion	Right Side		Left Side		Worse Side	
	No. at Risk*	Prevalence, %	No. at Risk*	Prevalence, %	No. at Risk*	Prevalence, %
Soft indistinct drusen	3268	12.2	3296	12.3	3379	17.6
Moderate-sized drusen	3268	13.7	3297	14.6	3379	20.5
Hyperpigmentation	3282	9.7	3308	10.4	3387	14.8
Retinal pigment epithelial depigmentation	3273	5.4	3298	5.3	3385	8.2
Pigmentary abnormalities	3274	10.3	3300	10.8	3384	15.3
Early age-related maculopathy	3224	16.3	3252	17.0	3318	23.5
Geographic atrophy	3244	0.6	3269	0.5	3340	0.7
Exudative macular degeneration	3245	0.6	3280	0.9	3371	1.2
Late age-related maculopathy	3265	1.3	3297	1.4	3381	1.9
Hearing loss	3393	36.8	3393	39.6	3397	45.0

**Number may vary, in part due to missing data.*

Table 2. Age- and Sex-Adjusted Rates of Hearing Loss for ARM and Its Lesions in the Study Population*

ARM Lesions in the Worse Eye	No. at Risk	Prevalence, %	Age- and Sex-Adjusted Rate of Hearing Loss	
			Prevalence, %	*P*
ARM lesions				
Soft indistinct drusen				
Absent	2785	41.2	44.4	.12†
Present	594	62.8	47.9	
Moderate-sized drusen				
Absent	2684	40.6	44.3	.07†
Present	695	61.9	48.2	
Increased retinal pigment				
Absent	2885	42.0	44.5	.25†
Present	502	61.6	47.3	
Retinal pigment epithelial depigmentation				
Absent	3107	43.0	44.6	.30†
Present	278	65.8	47.8	
Pigmentary abnormalities				
Absent	2865	41.8	44.4	.16†
Present	519	61.7	47.7	
Geographic atrophy				
Absent	3318	44.2	44.8	.83‡
Present	22	86.4	42.4	
Exudative macular degeneration				
Absent	3330	44.3	44.8	.43‡
Present	41	90.2	51.9	
ARM severity				
No ARM	2518	39.8	44.0	.07§
Early ARM	779	57.8	47.1	
Late ARM	63	88.9	50.6	

**ARM indicates age-related maculopathy.*
†Determined using χ^2 test for association.
‡Determined using Fisher exact test.
§Determined using Mantel-Haenszel χ^2 test for overall trend.

After controlling for age and sex, there were small (15%-23%) excesses of hearing loss in persons with early ARM lesions that were not statistically significant ($P>.05$) (**Table 3**). After adjusting for age and sex, the odds for hearing loss were 3.76 times greater in those with exudative macular degeneration compared with those without exudative ARM. Similarly, the odds for hearing loss were 3.15 times greater in those with late ARM compared with those without late ARM. These relations did not change after controlling for other potentially confounding factors (eg, cigarette smoking status, history of occupational noise exposure, and history of cardiovascular disease) (Table 3).

Sex-specific, age-adjusted, logistic regression models demonstrated that, for women, there were significant ($P<.05$) associations between hearing loss and soft indistinct drusen (odds ratio [OR]=1.34; 95% confidence interval [CI]=1.01-1.77), exudative macular degeneration (OR=3.27; 95% CI=1.05-10.16), and late ARM (OR=2.65; 95% CI=1.09-6.44). No significant associa-

Table 3. Odds Ratios of Hearing Loss in Worse Ear in Participants With Various Maculopathy Lesions in Worse Eye in the Study Population

Lesion	Odds Ratio* (95% Confidence Interval)	Odds Ratio† (95% Confidence Interval)
Soft indistinct drusen	1.15 (0.92-1.44)	1.16 (0.93-1.45)
Moderate-sized drusen	1.16 (0.94-1.42)	1.15 (0.93-1.42)
Hyperpigmentation	1.16 (0.92-1.46)	1.16 (0.92-1.46)
Retinal pigment epithelial depigmentation	1.23 (0.91-1.67)	1.25 (0.92-1.69)
Pigmentary abnormalities	1.18 (0.94-1.48)	1.17 (0.93-1.48)
Geographic atrophy	2.30 (0.60-8.84)	2.33 (0.61-8.84)
Exudative macular degeneration	3.76 (1.24-11.38)	3.79 (1.25-11.48)
Early age-related maculopathy	1.12 (0.92-1.35)	1.11 (0.91-1.35)
Late age-related maculopathy	3.15 (1.34-7.42)	3.17 (1.35-7.45)

**Based on logistic regression; adjusted for age and sex.*
†Based on logistic regression; adjusted for age, sex, and history of smoking, occupational noise exposure, and cardiovascular disease.

tions were found between hearing loss and signs of early ARM in men. There were too few men (n=20) with late ARM to evaluate its association with hearing loss.

We wished to know whether significant relations between ARM and hearing sensitivity would be observed if hearing performance was treated as a continuous outcome. To assess this, hearing sensitivity was defined as the PTA of hearing thresholds at 500, 1000, 2000, and 4000 Hz in the worse ear. Results from age- and sex-adjusted analysis of covariance models demonstrated that exudative macular degeneration and late ARM were significantly ($P<.05$) related to hearing sensitivity. Specifically, those with exudative macular degeneration had a PTA that was 10.2 dB higher on average than those without this lesion (37.9 vs 27.7 dB; $P<.001$). Similar results were found for late ARM (34.3 vs 27.7 dB; $P=.002$). Effects for other maculopathy lesions were not statistically significant.

Our research focuses on the relation between ARM and hearing loss in the frequency range important for understanding speech (500-4000 Hz). In addition, we examined this relation for higher frequencies, defining hearing loss as a PTA of hearing thresholds at 4000, 6000, and 8000 Hz greater than 40-dB hearing level in the worse ear. Results from logistic regression models, adjusting for age and sex, revealed a significant association between high-frequency hearing loss and moderate-sized drusen (OR=1.36; 95% CI=1.07-1.74), pigmentary abnormalities (OR=1.36; 95% CI=1.04-1.79), and early ARM (OR=1.30; 95% CI=1.04-1.62), but no relation for late-stage lesions (data not shown).

COMMENT

Age-related maculopathy (25.4%) and hearing loss (45.0%) were prevalent in the Beaver Dam population. Both conditions were found in 39.5% of the population 75 years or older. Based on these data, we estimate that there are 5 126 000 Americans 75 years or older who have signs of ARM and hearing loss. As ARM is an important cause of loss of vision, and as hearing loss often is associated with difficulty in everyday communication, the high frequencies of sensory comorbidity may affect independent functioning of people as they age.

Signs of late ARM were related to the presence of hearing loss. When late ARM was present in either eye, the odds for hearing loss were approximately 3 times greater than in those without late ARM. Similar factors (ie, smoking, cardiovascular disease, and oxidative damage) have been postulated as possible causes for coexistent late ARM and age-related hearing loss.[29-31] However, in our study, the association between late ARM and hearing loss remained after controlling for some of these factors. To our knowledge, no other data are available describing a similar association between late ARM and hearing loss. We found small, statistically nonsignificant, positive relationships between soft drusen, pigmentary abnormalities, and hearing loss. The reason for an association of late but not early ARM lesions with hearing loss is not known.

One limitation in assessing the association between these conditions is that ARM is defined by anatomic changes detected on fundus photographs, whereas hearing loss in older persons may be due to changes in middle ear cochlear or neural (auditory nerve) function. Central auditory processing also may be compromised with advancing age. Moreover, hearing loss measured by audiometry is insensitive to early cochlear and neural insult that may be analogous to early ARM. This would tend to weaken the association between hearing loss and ARM. Despite our inability to precisely measure the anatomic location of hearing loss, however, we found an association of hearing loss with late ARM.

Age-related hearing loss usually first affects sensitivity for high-frequency sounds. With time, there may be a gradual decline in hearing thresholds in the speech frequencies. Thus, high-frequency hearing loss may represent an early stage of age-related hearing loss. In analyses defining hearing loss as a PTA of more than 40 dB for the frequencies 4000, 6000, and 8000 Hz, there was a significant association between early but not late ARM and hearing loss. This is the opposite of the results when hearing loss in the traditional speech frequencies was evaluated (association between late but not early ARM and hearing loss). These results suggest that the lack of consistent relations between late and early ARM and hearing loss may reflect the limitations of comparing different stages of these disease processes.

Factors other than age may account for hearing loss in our study. Clearly, not all hearing loss is age related. In any cross-sectional study, hearing loss may have been present from birth or due to a childhood illness, genetic syndrome, or trauma. This, in turn, would weaken the ability to find a relationship with various factors if one existed. However, after removing a group of participants with probable non–age-related hearing loss and controlling for a history of occupational noise exposure, the association between hearing loss and late ARM remained.

In summary, an association between late ARM and hearing loss was found. The reasons for this association are not known at this time and require further study.

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Human Herpesvirus 8 DNA Sequences in Blistering Skin From Patients With Pemphigus

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Background: Human herpesvirus 8 (HHV-8) has been detected in Kaposi sarcoma (KS) and other lesions in patients both seropositive and seronegative for the human immunodeficiency virus (HIV). Kaposi sarcoma has been reported to develop in a disproportionate number of patients with pemphigus. Since HHV-8 is so strongly associated with KS, we wondered whether HHV-8 is present in pemphigus lesions from patients without KS or HIV infection. Pemphigus lesions and skin from healthy individuals were coded in a blinded fashion. Tissue-extracted DNA was tested using polymerase chain reaction, Southern blot hybridization, and automated sequencing of the polymerase chain reaction products for the presence of HHV-8 DNA. Six patients had pemphigus foliaceus, 6 had pemphigus vulgaris, and 2 had KS; 10 healthy individuals were used as controls. All 24 patients were HIV seronegative.

Observation: Lesional skin from 4 of the 6 patients with pemphigus vulgaris, all 6 of the patients with pemphigus foliaceus, and both positive controls (KS) tested positive for HHV-8 DNA. Furthermore, the HHV-8 DNA sequences for $KS330_{233}$ differed between all 6 DNA specimens from pemphigus foliaceus, while 3 of the 4 DNA specimens from pemphigus vulgaris were identical. However, HHV-8 DNA was absent in all normal human skin analyzed.

Conclusions: This report expands the spectrum of lesions found to contain HHV-8 DNA sequences and suggests that HHV-8 might have trophism for pemphigus lesions. (*Arch Dermatol. 1997;133:1247-1251*)

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