Association of Age Related Macular Degeneration and Age Related Hearing Impairment

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Abstract

Purpose: To evaluate the association between age-related macular degeneration (ARMD) and sensory neural hearing impairment (SHI).

Methods: In this case-control study, hearing status of 46 consecutive patients with ARMD were compared with 46 age-matched cases without clinical ARMD as a control group. In all patients, retinal involvements were confirmed by clinical examination, fluorescein angiography (FA) and optical coherence tomography (OCT). All participants were examined with an otoscope and underwent audiological tests including pure tone audiometry (PTA), speech reception threshold (SRT), speech discrimination score (SDS), tympanometry, reflex tests and auditory brainstem response (ABR).

Results: A significant ($P = 0.009$) association was present between ARMD, especially with exudative and choroidal neovascularization (CNV) components, and age-related hearing impairment primarily involving high frequencies. Patients had higher SRT and lower SDS against anticipated presbycusis than control subjects. Similar results were detected in exudative, CNV and scar patterns supporting an association between late ARMD with SRT and SDS abnormalities. ABR showed significantly prolonged wave I and IV latency times in ARMD ($P = 0.034$ and 0.022, respectively). Average latency periods for wave I in geographic atrophy (GA) and CNV, and that for wave IV in drusen patterns of ARMD were significantly higher than controls ($P = 0.030$, 0.007 and 0.050, respectively).

Conclusion: The association between ARMD and age-related SHI may be attributed to common anatomical components such as melanin in these two sensory organs.

Keywords: Age Related Macular Degeneration; Sensory Neural Hearing Impairment; Retinal Pigment Epithelium; Pigmentary Disorder; Melanin

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INTRODUCTION

Age-related macular degeneration (ARMD) is a progressive degenerative macular disorder which may lead to loss of central vision and eventually blindness.

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ARMD is the most common cause of blindness among the elderly in developed countries.[1-4] The global or pooled prevalence of early, late, and any ARMD has been estimated as 8.01% worldwide.[5] Two types of exudative (wet) and non-exudative (dry) ARMD have been defined. The latter consists of 80-90% of patients suffering from ARMD. Generally, both eyes are involved, but at the beginning, the condition may appear in one eye. The diagnosis is made by clinical examination, fluorescein angiography (FA) and optical coherence tomography (OCT).

The exact etiology of ARMD is not well understood; however, during the last three decades, the most important basic role has been attributed to retinal pigment epithelial (RPE) disorders. Decreased natural defense mechanisms followed by increased oxidative stress during the aging process seem to be the most important mechanism in RPE damage.[6-8] Melanin in RPE cells plays an important protective role against oxidative stress. Significant melanin dysfunction or abnormality may eventually lead to apoptosis of RPE cells, resulting in neural retinal cell death and eventually blindness.[9-11] Melanin dysfunctions play a critical role in the pathogenesis of ARMD, and there are some studies that suggest a relationship between hearing impairment, and iris and skin pigmentary disorders.[12-14]

The cochlear structure of the inner ear includes the organ of corti and stria vascularis as the major sensory organs. Melanocytes are present in nearly all parts of the inner ear, but atria vascularis contains the highest amount of melanin in the cochlea.[15] Melanin protects cochlea and stria vascularis against oxidative stress.[16] Age-related deterioration of stria vascularis is more severe in the base and apex of the cochlea, gradually aggravated by aging.[17] Interestingly, in some pigmentary disorders, simultaneous visual and hearing impairments are encountered such as in Usher and Waardenburg syndromes.[18,19]

Although the development of ARMD seems to be multifactorial (inflammation, autoimmunity and polymorphisms of complement factor, deposition of extra-cellular materials on Bruch's membrane, certain genotypes, and lifestyle risk factors[20-25]), the prevalence of ARMD is greatly related and dependent on aging and its prevalence differs from 0% in population younger than 55 years to 18.5% in individuals over 85 years of age.[26] As melanin enriched cells share anatomical structures in both the outer retina and inner ear, we hypothesized that ARMD and SHI may be parts of a common melanin dysfunction.

METHODS

In this case-control study, the hearing status of 46 consecutive patients with ARMD was compared with 46 age-matched controls without clinical ARMD. All subjects were referred to Mustafa and Negah Eye Hospitals during a 15-month period. The sample size was calculated based on the standard sample size formula and similar studies in the literature.[27] A retina subspecialist confirmed the diagnosis in each patient by precise direct and/or indirect ophthalmoscopy, FA (Heidelberg eye explorer HRA2, Spectralis, Heidelberg, Germany) and OCT (Topcon 3D OCT 1000, Topcon Corporation, Tokyo, Japan) using the early age-related maculopathy (ARM) international classification system and Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS).[8,28] Based on this classification, in one or both eyes, patients who had only or predominantly drusen were considered as the drusen group. Those with only or predominantly geographic changes were considered as the geographic atrophy (GA) group. Those with or without the previous patterns but with neovascular changes were considered as the choroidal neovascularization (CNV) group, and advanced cases with staining but no active leakage on FA were considered as scar ARMD.

The study protocol was approved by the review board/ethics committee of Shahed University of Medical Sciences, Tehran, Iran. The control group was matched in terms of age and gender, and was evaluated to rule out visual and hearing impairment and entered the study if they had eligibility and provided informed consent. All cases were aged over 55 years and had at least one eye with ARMD. Based on history, patients with congenital, neonatal, infantile, traumatic or sudden hearing loss and ruptured tympanic membrane on otoscopic examination were excluded. Other exclusion criteria were history of traumatic or congenital retinal disorders, diabetic retinopathy confirmed by clinical examination and FA, and any retinal or auditory problems related to toxic medications such as furosemide or chloroquine.

Audiometric tests included pure tone air and bone conduction audiometry at frequencies of 250, 500, 1000, 2000, 4000 and 8000 Hertz (Hz), speech recognition test (SRT) and speech discrimination score (SDS) (Clinical Audiometer AC33, Inter Acoustic Company, Denmark), and tympanometry and reflex tests (Impedance Audiometer AZ26, Inter Acoustic Company, Denmark). Bone conduction was measured with a bone vibrator device on the mastoid bone. Types of pure tone audiometry (PTA), degrees of hearing impairment and hearing levels at each frequency were recorded. Air bone gaps greater than 5 decibels (dB) were considered as conductive hearing loss. Hearing impairment in either ear was defined when hearing threshold was more than 20 dB above normal values at any frequency (from 250 to 8,000 Hz). Hearing levels were classified from N1 to N6 as normal (equal or lower than 20 dB), mild (21-40 dB) hearing impairment, moderate (41-55 dB) hearing impairment, moderate to severe (56-70 dB) hearing impairment, severe (71-90 dB) hearing impairment and profound (>90 dB) hearing impairment, respectively.

SRT was defined as the hearing threshold when the patient could repeat at least 50 percent of two syllable words and SDS score was defined as the percentage of one syllable words which the case could recognize at 40 decibels intensity. Standard tympanometry using low-frequency probes was performed in a quiet room and then extra tones were used for measuring reflex tests of the stapedius muscle. Auditory brainstem response (ABR) was performed to localize the site of hearing loss. The latency period of waves (I, II, III, IV, and V) and the latency period of inter peak waves (I-III, I-V, and III-V) in ABR were analyzed between groups using seeking ABR. ABR was done with 0.2 μv/D amplitude at 110 dB/65 dB and 1 ms/D stimulation rate and 2,000 repetition.

Data were analyzed with SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) using statistical tests such as Chi-square, *t* test, analysis of variance (ANOVA), Mann-Whitney, Kruskal-Wallis and general linear models to drawing audiograms.

RESULTS

Out of 46 subjects with ARMD, 30 patients had bilateral and 16 patients had unilateral involvement; a total of 76 eyes affected with ARMD were considered for statistical analysis. An equal number of male and female subjects were enrolled in the case and control groups. Mean age was 71.41 (range, 56 to 93) years. There were no significant difference concerning age ($P = 0.92$) or presence of systemic disorders such as diabetes mellitus ($P = 0.12$), hypertension ($P = 0.83$), hyperlipidemia ($P = 0.64$), ischemic heart disease ($P = 0.77$), chronic kidney disease ($P = 0.74$), smoking habits ($P = 0.67$) and drug use ($P = 0.74$) between the two groups. The frequencies of different types of ARMD are summarized in Table 1.

Significant differences were observed in terms of hearing impairment between ARMD patients and control cases (72.8% vs. 54.3%, $P = 0.009$). Simultaneous visual and hearing impairment in subjects older and younger than 75 years was significantly higher in cases than controls ($P < 0.001$). Tinnitus was significantly more frequent in female cases than female controls, and male cases than male controls ($P = 0.047$ and 0.007,

respectively). Disequilibrium was also more common in cases as compared to controls ($P = 0.018$). Average SRT and SDS values were significantly different in cases vs. controls, in non-exudative vs. exudative ARMD, and between various subtypes of ARMD (CNV, scar, drusen and GA) ($P = 0.012$, <0.001 and < 0.001 for SRT; $P < 0.001$, 0.002 and 0.001 for SDS, respectively).

Different types of PTA including normal, conductive, sensorineural and mixed were significantly different between the study groups ($P = 0.026$). Figure 1 shows that normal and conductive types of PTA were less common, but sensorineural PTA was significantly more frequent in cases than controls ($P = 0.001$). Due to the rarity of conductive and mixed types in both study groups and no air bone gap in others, sensory levels of hearing were considered in both groups. We noticed that hearing thresholds at frequencies of 250, 4,000 and 8,000 Hz were significantly higher in cases than controls [Table 2]. The average descending level of all frequencies in exudative ARMD was significantly higher than non-exudative ARMD [Table 3]. The average degrees of hearing impairment in various subtypes of ARMD (drusen, geographic atrophy, scar and CNV) were significantly different from the controls. Interestingly, the most marked deterioration in hearing levels at all frequencies, especially at 250 Hz, belonged to the CNV subtype of ARMD [Table 4].

We noticed that decadence of all frequencies particularly at high and low frequencies appeared in cases aged more than 75 years; however, this was not the case for low frequencies in matched controls with or without presbycusis ($P = 0.001$). Audiograms of cases and controls, and ARMD subtypes were compared using general linear models [Figures 2-4]. Tympanometry (air
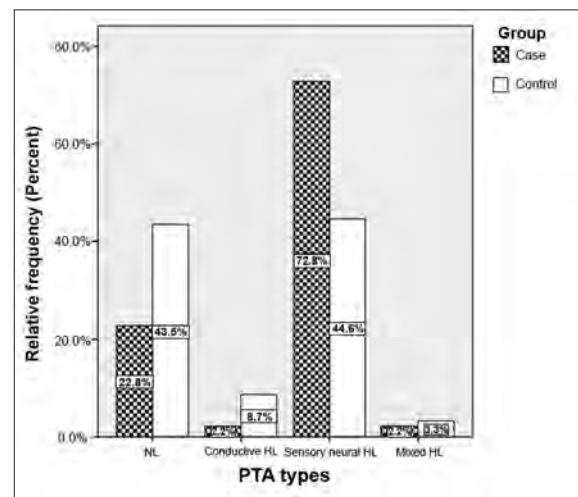

Figure 1. Relative frequency of PTA types in cases and control. Significantly higher numbers of controls were normal (NL) or had conductive defects in hearing status; in contrast, significantly higher numbers of sensorineural hearing impairment were observed in ARMD patients as compared to controls. NL, normal; HL, hearing loss.

Table 1. Frequency of different subtypes of age related macular degeneration among cases			
ARMD	**FA patterns (%)**	**Types of ARMD**	***n* (%)**
ARMD involved eyes (*n*=76)	Nonexudative 60 (79)	Only drusen	49 (64.5)
		GA	11 (14.5)
	Exudative 16 (21)	CNV	14 (18.5)
		Scar	2 (2.5)
ARMD, age related macular degeneration; GA, geographic atrophy; FA, fluorescein angiography; CNV, choroidal neovascularization; n, number			

Table 2. Mean thresholds of hearing levels at different frequencies decibel in cases and controls

Frequency (Hz)/groups	Mean (dB)	SD	SD mean error	P*
250				
Case	20.43	16.94	1.76	<0.001
Control	8.15	6.98	0.72	
500				
Case	15.2	15.24	1.58	0.111
Control	11.84	11.16	1.16	
1000				
Case	19.38	18.45	1.92	0.144
Control	15	15.67	1.63	
2000				
Case	24.5	22.36	2.33	0.096
Control	19.34	17.29	1.8	
4000				
Case	42.33	25.79	2.68	0.021
Control	27.09	20.46	2.13	
8000				
Case	49.92	27.34	2.85	P=0.002
Control	32.16	26.82	2.79	

SD, standard deviation. Mean thresholds of hearing levels at low (250 Hz) and high frequencies (4000 and 8000 Hz).*Based on *t*-test analysis

Table 3. Mean thresholds of hearing levels in nonexudative and exudative age related macular degeneration age related macular degeneration

Frequency (Hz)	Types of ARMD	Mean	SD	P*
250	Nonexudative	17.57	13.11	<0.001
	Exudative	33.94	23.3	
500	Nonexudative	13.41	12.9	0.006
	Exudative	24.31	20.65	
1000	Nonexudative	16.08	16.22	<0.001
	Exudative	32.84	21.55	
2000	Nonexudative	21.97	21.23	0.012
	Exudative	36.52	24.15	
4000	Nonexudative	39.85	24.23	0.017
	Exudative	55.78	28.29	
8000	Nonexudative	47.35	26.33	0.036
	Exudative	62	27.12	

ARMD, age related macular degeneration; SD, standard deviation. *Based on *t*-test analysis

conduction) showed no significant differences between the study groups.

Using seeking ABR, the latency time of waves I and IV were significantly prolonged in cases as compared to controls (P = 0.034 and 0.022 respectively). Average latency periods for waves I in GA and CNV, and wave IV in drusen subtypes of ARMD were significantly higher in cases as compared to controls (P = 0.030, 0.007 and 0.050 respectively).
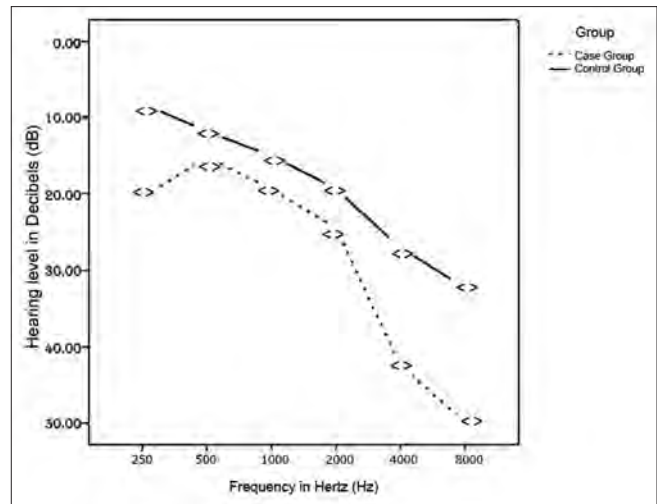

Figure 2. Comparison of audiograms in ARMD patients and controls. The decline in sensorineural hearing levels at different frequencies (dB) in cases as compared to controls was especially prominent at lower and higher frequencies. The lines indicate sensorineural hearing threshold levels in both groups. dB, decibel; Hz, hertz.

DISCUSSION

The present study revealed that ARMD had a significant association with SHI, and that these patients are more susceptible to develop hearing impairment at younger age. Few previous studies have shown this significant association between ARMD and hearing impairment.[27,29,30] We also outlined the hypothesis of possible similar roles for melanin in development of these two disorders in the retina and inner ear. Moreover, subjective signs of hearing impairment in ARMD patients were investigated. Tinnitus was more frequent in female subjects as compared to male cases and female controls. This may be due to the higher prevalence of ARMD in female patients, although systemic mechanisms may interfere with neural input and output in tinnitus.[31] Furthermore, disequilibrium was more prevalent in cases than controls which may be due to dysfunction of equilibrium structures (vestibular dark cells in vestibular end organ). These findings support the possible role of cochlear dysfunction in ARMD patients.

SRT and SDS displayed increased hearing threshold in cases as compared to controls. This is suggestive of a common underlying pathology for visual and hearing impairment in ARMD patients. Increased averaged SRT in female cases as compared to matched controls may be indicative of the greater susceptibility of females to simultaneous hearing and visual impairment. Higher average SRT in CNV and scar patterns of ARMD supports an association between late ARMD and SRT. Lower average SDS in cases than controls and in female cases than in female controls, has a similar explanation.

Table 4. Mean thresholds of hearing levels in various angiographic patterns in cases and controls

Angiographic patterns (*n*)	Frequency 250	Frequency 500	Frequency 1000	Frequency 2000	Frequency 4000	Frequency 8000
Drusen (49)						
Mean	18.67	14.26	16.63	24.08	42.14	49.91
SD	1.33	1.37	1.79	2.25	2.48	2.66
Control (92)						
Mean	8.15	11.84	15.00	19.34	27.09	32.16
SD	6.98	11.16	15.67	17.29	20.46	26.82
*P**	<0.001	0.16	0.49	0.11	<0.001	0.001
GA (11)						
Mean	15.00	10.09	14.81	13.36	30.00	36.36
SD	1.09	8.78	9.52	1.13	1.26	1.35
Control (92)						
Mean	8.15	11.84	15.00	19.34	27.09	32.16
SD	6.98	11.16	15.67	17.29	20.46	26.82
*P**	0.02	0.70	0.98	0.31	0.73	0.75
CNV (14)						
Mean	37.50	28.00	38.78	42.71	63.57	68.78
SD	2.50	2.10	2.01	2.18	2.79	2.76
Control (92)						
Mean	8.15	11.84	15.00	19.34	27.09	32.16
SD	6.98	11.16	15.67	17.29	20.46	26.82
*P**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Scar (2)						
Mean	35.00	27.50	25.00	40.50	50.00	50.00
SD	0.00	2.47	2.82	2.75	0.00	1.41
Control (92)						
Mean	8.15	11.84	15.00	19.34	27.09	32.16
SD	6.98	11.16	15.67	17.29	20.46	26.82
*P**	<0.001	0.046	0.34	0.08	0.14	0.40

GA, geographic atrophy; CNV, choroidal neovascularization; SD, standard deviation. *Based on analysis of variance test
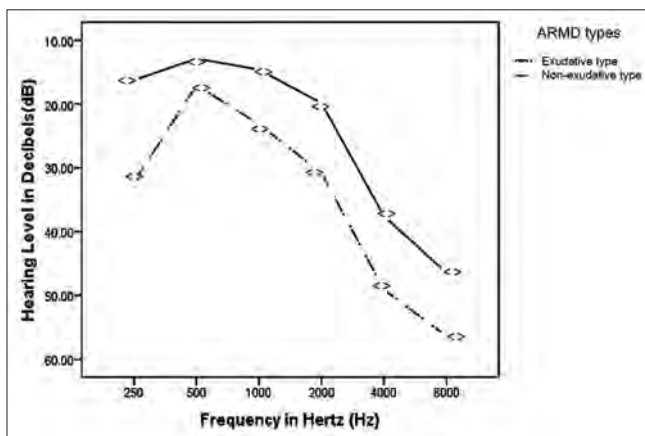

Figure 3. Comparison of audiograms in exudative and non-exudative types of ARMD. The decline in sensorineural hearing levels at different frequencies (dB) in exudative as compared to non-exudative types of ARMD was prominent at lower frequencies. The lines indicate sensorineural hearing threshold levels in both groups. dB, decibel; Hz, hertz; ARMD, age-related macular degeneration.

As an indicator, PTA analysis showed more SHI in ARMD patients. This test may also help predict vulnerability of younger patients to develop SHI in the future. Moreover, our study demonstrates an increased degree of hearing impairment in exudative, CNV and scar patterns of ARMD that is suggestive of association between late ARMD with SHI. Bozkurt et al and Klein et al proposed that late ARMD was more likely associated with hearing impairment, however, they did not weigh different stages of ARMD based on FA against diverse audiologic tests. They also did not explain the mechanisms by which late ARMD and hearing impairment may theoretically be associated.[27,32]

The current study showed more significant hearing impairment in cases than the controls at frequencies of 250, 4,000 and 8,000 Hz. In Klein et al study as well, cases showed more decline at high frequencies than controls. In our study, hearing impairment at 250 Hz was mostly paired with exudative types and CNV patterns. Interestingly, Liew et al showed that decadence
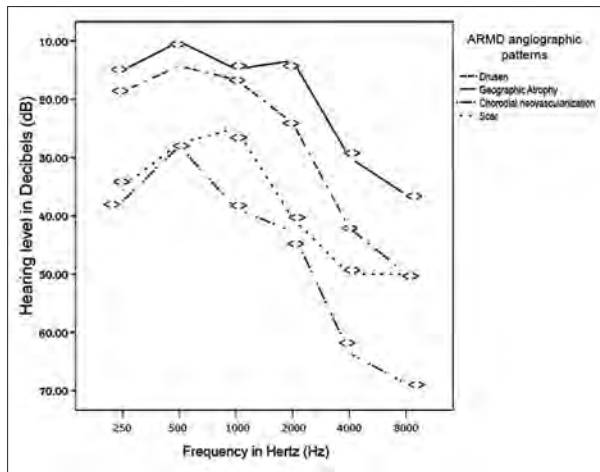
Figure 4. Comparison of audiograms in different angiographic patterns of ARMD. Note the decline in sensorineural hearing levels at different frequencies (dB) in various angiographic patterns of ARMD patients. The lines indicate sensorineural hearing threshold levels in both groups. dB, decibel; Hz, hertz; ARMD, age-related macular degeneration.

of low frequencies in age-related hearing impairment is correlated with microvascular retinopathies particularly in female subjects.[33] Meanwhile, CNV lesions were more associated with decay in sensation at all frequencies. This is in parallel with Chia and Klein's findings regarding the stronger correlation between late ARMD and increased hearing loss, however; they did not evaluate stages of ARMD by retinal angiography against diverse audiologic tests.[29,32] Overall, it seems that CNV angiographic patterns are related to higher SRT, lower SDS, more severe hearing impairment and more decadence at all frequencies. We noticed that decadence of all frequencies especially at high and low frequencies appeared in cases older than 75 years. This finding was not encountered for lower frequencies (i.e. 250 Hz) in age-matched controls with or without presbycusis.

Stria vascularis in the corti structure of the cochlea is the main structure including melanocytes.[34] The number of corti structures and melanocytes is lower at the base as compared to the apex of the cochlea. Lower melanin concentration makes the cochlear base more susceptible to oxidative stress and lipofuscin aggregation.[35] Age-related destruction of stria vascularis is greater at the base (high frequencies) but by aging, gradually extends to the apex (low frequencies) and then, all parts of the cochlea (endocochlear potential).[17] On the other hand, the macula contains many RPE cells[36,37] and melanin within the RPE cells protects photoreceptors against oxidative stress.[38,39] Melanin dysfunction as the most important event in ARMD, caused low to moderate visual loss and eventually blindness. Through aging, the amount of melanin in RPE cells decreases and conversely lipofuscin granules depositions increase.[36,40,41] In fact,

RPE cells and photoreceptors act as a functional unit for the visual system. Therefore, melanin destruction induced by oxidative stress might account as a possible cause for concurrent visual and hearing impairment in the elderly.

Independent of the patients' cooperation, ABR is helpful for diagnosis of retro-cochlear hearing problems and therefore is very advantageous in old patients who are may be poorly cooperation. In ABR, a normal wave I indicated normal cochlear nerve and normal wave IV represents integrity of the neural signal pathways from the cochlear nucleus to the superior olivary complex (SOC) and possibly trapezoid body in the central neural system.[42] Prolongation of waves I and IV in the cases also verifies the concurrent cochlear system pathology in ARMD patients.

Despite the effects of genotype and life style on ARMD which warrants larger surveys, small sample size and expensive paraclinical examinations were the most important limitations of the present study. This problem led to the low number of cases for scar patterns of ARMD that affected the validity of statistical tests in this subgroup. However; this restriction did not affect the overall conclusion of the study. To establish an actual relationship between ARMD and SNHI, pathological based investigations are recommended.

In summary, findings of our study indicate an association between ARMD and SHI. Although the results of the present study are not sufficient to conclude an association between melanin dysfunction and ARMD, as a hypothesis, we would like to draw attention to the possibility of a common melanin dysfunction in RPE cells and the auditory system.

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Conflicts of Interest

There are no conflicts of interest.

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