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LOSS OF OTOLITH FUNCTION WITH AGE IS ASSOCIATED WITH INCREASED POSTURAL SWAY MEASURES

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Abstract

Background—Loss of balance and increased fall risk is a common problem associated with aging. Changes in vestibular function occur with aging but the contribution of reduced vestibular otolith function to fall risk remains unknown.

Methods—We examined a population of 151 healthy individuals (aged 21–93) for both balance (sway measures) and otolith counter-rolling (OCR) function. We assessed balance function with eyes open and closed on a firm surface, eyes open and closed on a foam surface and OCR during ± 20 degree roll tilt at 0.005 Hz.

Results—Subjects demonstrated a significant age-related reduction in OCR and increased postural sway. The effect of age on OCR was greater in females than males. The reduction in OCR was strongly correlated with the mediolateral measures of sway with eyes closed. This correlation was also present in the elderly group alone, suggesting that aging alone does not account for this effect.

Conclusions—OCR decreases linearly with age and at a greater rate in females than males. This loss of vestibular otolith-ocular function is associated with increased mediolateral measures of sway which have been shown to be related to increased risk of falls. These data suggest a role for loss of otolith function in contributing to fall risk in the elderly. Further prospective, longitudinal studies are necessary to confirm these findings.

Keywords

Vestibular; Aging; Sex Differences; Falls; Balance; Otolith

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Introduction

Aging is associated with a number of physiological changes including loss of balance [12]. Loss of balance can be the result of decrements in a number of systems including vestibular, proprioceptive, vision and musculoskeletal. Previous work has demonstrated decrements in vestibular function including postural sway [21] and visual-vestibular ocular reflexes [13]. Measures of otolith function, including otolith-ocular reflex during off-vertical axis rotation [8], linear vestibulo-ocular reflex [30] and vestibular evoked myogenic potentials[2], have all demonstrated age related declines.

Concurrent with loss of balance with aging is the increased incidence of falls in elderly individuals [29]. Falls are one of the leading causes of injury in adults with over 30% of people aged 65 and over living independently experiencing falls each year and once they experience a fall, subsequent risk of falls is increased [32] ultimately leading to an increased morbidity and mortality rate in elderly people [16].

While the causes of age-related postural instability and falls are likely multi-factorial, the role of otolith loss has not been well studied. We report a cross-sectional study of the relationship between measures of otolith-ocular reflexes and postural control as a function of both age and gender. For otolith-ocular function we evaluated the modulation of ocular torsion during sinusoidal roll tilt [referred to as ocular counter-rolling or OCR, 5]. For balance control we evaluated postural sway with eyes open and closed and while standing on a fixed or unstable support surface to disrupt somatosensory feedback. We hypothesized vestibular loss as a common mechanism for the decline in both otolith-ocular and vestibulo-spinal pathways with aging, and predicted a correlation between OCR and postural sway measures [25].

Methods

Subjects

One hundred and fifty one subjects (97 Females, 54 Males) aged 21–93 were recruited for a study of balance and vestibular function. Distribution of subjects was greater for the twenties and seventies (Fig. 1A). Males were 48.9 ± 22.8 years, 84.6 ± 13.1 kgs, 176.8 ± 7.8 cms. Females were 51.5 ± 20.8 years, 65.9 ± 10.8 kgs, 160.2 ± 7.1 cms. All subjects were otherwise healthy individuals with no history of cardiovascular, ophthalmic, neurological or vestibular disorders, taking no medications for hypertension, hypercholesteremia, migraine, epilepsy or any vestibular disorder. Subjects provided signed consent to the experimental protocols that had been approved by the Institutional Review Board at Beth Israel Deaconess Medical Center and was in accordance with the Declaration of Helsinki.

Ocular Counter-rolling

OCR is a reflexive torsional eye movement response to roll head tilt that is related to otolith function [5] and is reduced in patients who lack otolith inputs.[19] Conjugate OCR that was measured in this study is primarily attributed to the utricular otolith in response to the change in the gravito-inertial vector as the head is rotated in the earth horizontal plane [4]. OCR can be influenced by several other factors, including changes in gaze direction,[10] fixation distance,[6] and visual field.[3] To minimize these confounding effects, OCR measurements in this study were performed with subjects in a completely dark room fixating on a red LED light (2 mm diameter) ~137 cm directly in front of them (e.g., in their line of sight). Binocular torsion was recorded with head upright, and then during passive tilting left and right in a chair ± 20 degrees at 0.38 deg/sec for 420 seconds (two full cycles). We have previously demonstrated that the OCR elicited at this low frequency and velocity during roll tilt about an Earth-horizontal axis is identical to that obtained during variable radius centrifugation without canal cues [18],

and therefore this response is primarily mediated by the otoliths with minimal input from the vertical canals. Head position was stabilized with an adjustable head holder. Eye movements were recorded using a head-fixed binocular video camera system (SensoMotoric Instruments). Small monochrome video cameras were used with near-infrared emitting diodes to allow eye recording in darkness (60 Hz). OCR was processed off-line using an eye tracking system previously described [28,35]. Horizontal and vertical eye position were derived from tracking the pupil center using a least squares fit to a clipped circular disk model, and torsional eye movements were derived by tracking natural landmarks in the radial pattern of the iris using a polar cross correlation function. The accuracy of the torsion measures has been estimated at <0.1 deg during visual fixation as used in this study [28]. Post-processing was done using custom-written MATLAB scripts (Mathworks). The scripts included the exclusion of segments during saccades or eye closure, and least squares regression to derive the OCR gain, the ratio of OCR amplitude to amplitude of roll tilt.

Balance Control

To assess postural sway, the modified clinical test of sensory interaction on balance (mCTSIB) was used [27]. This test requires subjects to stand quietly on a force plate (Model BP5050; Bertec) which measures the vertical ground reaction forces. The subject's center of pressure (COP) was computed directly from force transducers in the force plate sampled at 100 Hz. Center-of-Mass (COM) was estimated based on a 2nd order Butterworth filter (0.85 Hz cutoff) applied to the COP. The estimate of COM from COP using similar low-pass filters have been well correlated with other COM estimates during quiet standing based on comparison to kinematic data of multiple body segments [e.g., 9]. Instantaneous medial-lateral (ML) and anterior-posterior (AP) sway angles were then derived from COM and subject height. Postural stability was assessed during four sensory conditions:

1. Eyes open upon a firm surface
2. Eyes closed upon a firm surface
3. Eyes open upon an unstable surface (foam pad)
4. Eyes closed upon an unstable surface (foam pad)

The foam pad was 45 cm square $\times$ 13 cm thick, with a minimum density of 60 kg/m³. Subjects stood with shoes off wearing a safety harness attached to an overhead support with feet spaced shoulder width apart and arms at sides. The root mean square (RMS) of ML and AP sway position and sway area (ML, AP and total) were obtained for three trials of 30 seconds during each condition. Trials in which subjects stepped off the balance plate or were stabilized by the research assistant in the room were classified as falls.

To calculate sway area, summation of the sway values either the ML or AP direction was obtained to determine the total area in the ML or AP directions. Total sway area represented the summation of all sway motions to provide total area in which the sway had occurred. ML, AP and Total sway velocity, based on the change in sway and total sway path length were also calculated.

Statistical Analysis—The effects of age, gender and OCR on balance measures were assessed using a linear regression (SPSS) and differences between slopes were determined by a generalized linear model univariate analysis. For conciseness we have only reported AP and ML RMS and sway area and total sway area since changes in measures of sway velocity and total sway path length, showed similar patterns. To facilitate the comparison between otolith-ocular and balance measures, subjects were grouped according to OCR gains starting with <0.1 , and using bin intervals of 0.05, until 0.4. The average OCR gains and postural measures (e.g., RMS sway) for each of these groups were then used for regression and comparison. Data

were presented as mean $\pm$ SEM and levels of $p < 0.05$ were considered statistically significant. Balance trials with falls were not included in calculating mean sway parameters.

Results

Ocular Counter-rolling

Since OCR values were highly correlated between left and right eyes ($R^2 = 0.84$, $P < 0.001$, mean difference of 0.00 ± 0.03) values were averaged across eyes. While the variability was similar across decades (Fig 1A), there was a fairly uniform decline in OCR with age. There was no significant difference between sexes in mean OCR gain; however, decline in OCR with age was greater in females (compare Fig 1A left and right). The change in OCR per decade was significantly different between females (Fig 1B, Slope: -0.002 , $R: 0.50$, $P: 0.001$) and males (Slope: -0.001 , $R: 0.33$, $P: 0.02$, gender dependent effect $P = 0.001$).

Postural control Measures

While standing on a firm surface, there was a significant correlation in AP sway measures that increased from eyes open ($R^2 > 0.81$) to closed ($R^2 > 0.98$) as well as Total Sway ($R^2 = 0.64$ & 0.76). In contrast, there was no correlation between any of the AP measures and OCR during the same trials. When subjects stood on an unstable surface; however, all measures of balance were significantly correlated with OCR regardless of visual input (AP RMS & Area, $R^2 > 0.79$; ML RMS & Area & Total Sway Area, $R^2 > 0.86$).

As expected, the increase in ML RMS sway was more highly correlated with OCR since both occur in the roll plane. In contrast to the OCR measures, this trend for increased ML sway was not as uniform across decades (Fig 2 lower left). Note that the ML sway clearly was increased in the elderly (> 60 yrs). There was no significant effect of sex on any of the balance measures.

Falls

Of the 151 subjects, 10 (5 female, 5 male, 69 ± 17 years) had falls during the mCTSIB. Nine subjects fell during the eye closed on foam surface trials (most difficult condition) and one fell during both eyes open and closed on the foam surface. Subjects who fell had significantly greater sway measures in both the anterior posterior and mediolateral directions than subjects who did not fall. They also had significantly greater sway measures under all conditions than the elderly group in anterior posterior measures but not mediolateral sway. They also had significantly lower OCR (0.13 ± 0.08 vs. 0.18 ± 0.07 deg torsion/deg tilt, $P < 0.05$).

Relationship of Postural Control Measures associated with Fall Risk and Ocular Counter-Roll

Since previous work has found that ML RMS Sway during eyes closed on a firm surface is the best predictor of falls [15], we examined its relationship with OCR. Binning ML Sway RMS based on OCR values demonstrated an extremely strong correlation with ocular torsion (Figure 2).

To examine the role that aging may have played in these correlations, we performed the same comparison on just the older subjects. Figure 2 (right panel) demonstrates that while the age of the subjects did not differ across the OCR values, the mediolateral RMS Sway was still significantly correlated to OCR. This was also true of mediolateral sway area and total area.

Discussion

These data are the first to demonstrate two main findings: 1) There is a significant reduction in OCR linearly related to age that is greater in females than males; and 2) Reductions in otolith function are correlated to sway measures that are known risk factors for falls.

Our finding of a reduction in otolith-ocular function related to age (Fig. 1) is consistent with previous data from samples as large as a 1000 patients in which decreases in amplitude of the vestibular evoked myogenic potential (VEMP) were correlated with increasing age, reporting R^2 values of 0.21 [2] and 0.14–0.22, depending on stimulus intensity [20]. Therefore, the VEMP changes with age are comparable to OCR. These data in combination with our current data suggest that both otolith saccule (VEMP) and utricle (OCR) function decrease with age.

This decreased otolith function is likely due to morphological changes in the otoliths since both the number of hair cells and otoconia mass decrease with age [23]. Ross et al [26] demonstrated that the first change in the human vestibular system is demineralization of the otoliths. In addition, decreases in hair cell number have been found to be linearly related to age [17], consistent with our functional change in OCR. Increasing age is associated with decreased blood flow to the utricle [14] and attenuation of the neural response to otolith activation.[24] This is supported by the attenuated otolith-ocular responses of older subjects during linear acceleration stimuli.[8,31]

Our data are the first to demonstrate a sex difference in the age related decline in otolith-ocular function. While our female subjects demonstrated twice the decrease in OCR per decade than our males (~10% per decade for females compared to 5% for males), previous data using VEMP found no sex differences.[2] The reason for this difference remains unclear. One possibility is sex-dependent aging effects may differ between utricular (OCR) vs saccular (VEMP) function. Another possibility is that variability in the VEMP response may obscure the underlying sex difference. Further work is necessary to clarify this disparity.

The increase in postural sway in older subjects was first shown by Peterka and Black [21]. Subsequent to this initial publication, Black et al. reported over a three decade longitudinal study that changes in vestibular function decreased equally in each decade for this same population [1]. Interestingly, subjects in the lower 50th percentile showed decrements as early as the 2nd decade in females and the 4th decade for males.

Our data raise the question of whether loss of otolith function with age may be related to increased fall risk. While direct measures of falls during activities of daily living in these subjects were not performed, correlations to various balance measures that have been assessed with regards to fall risk were performed. We found a strikingly strong relationship between OCR and mediolateral sway with eyes closed on a firm surface (Figure 3). In a review of studies examining the use of force platform measures to predict falls, the best predictors were ML sway amplitude with eyes open and closed and the ML RMS [22]. Similarly in both an ambulatory and independent older population aged 62–96 years, ML sway with eyes closed was closely correlated with future falling risk and was able to predict falls in individuals with no recent history of falling [15]. Based on our current data, subjects with increased mediolateral sway also had significantly reduced OCR, suggesting the role of otolith function in falls appears to be an important area for consideration.

In addition in the subjects that were classified as having a fall during the balance trials, their OCR values were significantly lower than non-fallers. In fact, the only two subjects under age 50 that fell had OCR values of 0.03 and 0.09, which were extremely low for their age group. In addition, if we compare ML sway in fallers vs. non-fallers of the same age range, the only condition in which fallers had significantly greater sway was the eyes closed on a firm surface,

which is closely correlated to future falling risk [15]. These data suggest that even in young subjects, low OCR may be related to increased likelihood of falls when missing visual information.

If OCR is related to fall risk, based on our finding of a linear decrease in OCR, one would expect an increase in fall incidence with increasing age. Consistent with this, Era et al [7] found that sway measures increased in subjects from young to middle age to older subjects. Elderly patients (65–74) with bilateral vestibular loss had a 2.5x greater incidence of falls and unilateral patients had 1.6x greater incidence than aged matched controls [11]. Talbot et al [29], found that fall incidence increased from young to middle to older adults and that rates were higher in women than men. These data are consistent with our finding that the rate of decrease in OCR is greater in women.

However, the mechanism for these gender effects remains unclear. Previous data examining hair cell loss with aging found no sex differences [17]. One possible explanation is that loss of calcium from the otoconia could reduce the response of the otoliths. Consistent with this, women demonstrate significantly greater bone mineral density decreases throughout life than men [34]. In addition women with benign paroxysmal positional vertigo are more likely to have reduced bone mineral density than age matched controls [33]. Thus, indirect evidence may suggest a connection between bone loss and vestibular issues, however, further work is needed to determine the mechanism behind the greater OCR decrease in women.

One possible explanation for the correlation between OCR and measures of mediolateral postural sway may be the fact that both are impaired with age. However, if this were true then all measures of postural control function that were significantly correlated with increasing age, should positively correlate with reduced OCR gain. However, we found that anterior-posterior measures of sway were not correlated with OCR, even though they were correlated with age. In addition, we found that this strong relationship between ML sway and OCR was present in the elderly group alone even though there was not a wide spread in age in this group (Fig 2 lower right panel). Therefore, age alone does not explain this effect. These data suggest an independent role for OCR in the relationship between vestibular and postural control function. However, further longitudinal work using expanded measures of vestibular otolith function, postural sway and falls are necessary to substantiate this finding.

Limitations

While we found a reduction in OCR with age, this study used a cross sectional design. Thus, we cannot exclude the possibility that subjects with reduced OCR when older did not also have impaired function when younger. However, comparing the OCR of our under 30 and over 60 subjects, the likelihood that these values came from the same population is ~1.5% (T-test, $P=0.015$). In addition we did not directly measure falls in our subjects so we could not directly correlate OCR with fall risk.

The fact that OCR was significantly correlated with measures of ML sway is not surprising since both occur in the roll plane. It's important to note that this was the case for a natural stance in which subjects stood with feet spaced shoulder width apart, i.e., their base of support was greater in the ML direction. The effect would have been arguably more evident with a narrower stance such as tandem or standing on one leg. This further underscores the potential of OCR as a fall risk indicator since control of ML sway is important in dynamic movements such as navigating corners, which most vestibular impaired patients find challenging.

Summary

To our knowledge these are the first data to demonstrate that there is a linearly related age related decline in utricular otolith-ocular function that is correlated with mediolateral measures of postural sway. In addition our data demonstrate a greater age-related decrement in females than males. Finally, the loss of otolith function is correlated with impairment of postural control measures that are associated with increased risk of falls. This is consistent with our hypothesis that loss of utricular otolith function contributes significantly to fall risk in the elderly.

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Figure 1.

A) Age related changes in ocular counter-roll (OCR) for females (left) and males (right) Linear regression demonstrated significant declines in ocular counter-roll with age. Rate of decline in ocular counter-roll was statistically greater in the females. Solid lines represent linear regressions with dotted lines representing 95% confidence intervals. B) Slopes of decline in OCR with age. Females had significantly greater decreases in OCR per decade. *, significant difference between sexes, $P < 0.05$. Values are Mean $\pm$ SEM

Figure 2.

Relationship between ocular counter-roll (OCR) and mediolateral RMS sway (ML RMS sway) with eyes closed on firm and foam surface in all subjects (Left Panel) and older subjects (≥ 60 years, Right Panel). While OCR was significantly correlated to ML RMS sway, age did not differ among the older subjects at each OCR level, suggesting a role for OCR, independent of age. Values are Mean $\pm$ SEM grouped by OCR.