Original Paper

Effect of Transient Ischemic Attack on Hearing Thresholds of Older Subjects

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Key Words

Audiometric configurations • Hearing degeneration • Hearing thresholds • Transient ischemic attack

Abstract

The effects of transient ischemic attack (TIA) on pure tone average of low frequencies (PTA-low), of middle frequencies (PTA-mid), and of high frequencies (PTA-high), and audiometric configurations, which were classified by cluster analysis, were analyzed in older subjects. TIA showed significant positive association with PTA-high [β coefficient (β) $\pm$ standard error (SE) = 8.63 ± 2.81 , $p = 0.002$] after adjusting for age, sex, hypertension, and coronary artery disease. Besides, multinomial logistic regression for audiogram patterns showed that the moderate 8-kHz dip pattern ($\beta \pm SE = 1.70 \pm 0.78$, $p = 0.029$) was significantly more prevalent in the TIA group after adjusting for age, sex, and mean hearing level at all frequencies. We concluded that TIA without an obvious infarct lesion could contribute to hearing degeneration in older subjects, especially in high frequencies.

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Introduction

Age-related hearing impairment (ARHI), which is defined as progressive, symmetric age-related sensorineural hearing loss, is the most common sensory dysfunction in adults. It was generally accepted that cardiovascular disease (CVD) is associated with hearing degeneration [Van Eyken et al., 2007; Hwang et al., 2009], but the detailed relationship between the

affected frequencies and the entities of CVD remains a matter of debate. For example, hypertension (HTN) is associated with hearing loss in the low and middle frequencies in elderly women [de Moraes Marchiori et al., 2006; Rosenhall and Sundh, 2006] or at 1 kHz (middle frequency) only in adults [Agrawal et al., 2009]. ARHI was associated with myocardial infarction (MI) in women [Torre et al., 2005] and with an advanced stage of CVD in low frequencies [Friedland et al., 2009]. It seems that patients with mild forms of CVD, such as HTN, have poorer hearing in the low to middle frequencies, whereas those with advanced CVD, such as MI, show hearing loss mostly in the low frequencies. However, the effect of transient ischemic attack (TIA) on ARHI is seldom reported.

A TIA is a change in the blood supply to a particular area of the brain, resulting in a brief neurologic dysfunction that persists, by definition, for less than 24 h. Symptoms vary widely from person to person, depending on the area of the brain involved. When ischemia occurs in the vertebrobasilar system, it could be a sign of vertebrobasilar insufficiency. The most frequent symptoms include temporary loss of vision (typically amaurosis fugax); difficulty in speaking (aphasia); weakness on one side of the body (hemiparesis), and numbness or tingling (paresthesia), usually on one side of the body. Dizziness or poor balance are also symptoms related to TIA [Sylaja and Hill, 2009; Tyrrell et al., 2010].

The characteristics of TIA-related hearing dysfunction are still inconclusive. Hearing disorders in cervical vertigo were reversible [Hülse, 1994] but might impair auditory brain stem responses (ABRs) [Drake et al., 1990]. Sudden deafness might also rarely occur (in 8.0%) following vertebrobasilar insufficiency with obvious ischemic lesions on brain magnetic resonance imaging (MRI) [Lee and Baloh, 2005]. Furthermore, inner ear dysfunction in vertebrobasilar ischemic stroke mostly presented with unilateral sudden deafness [Yamasoba et al., 2001; Lee et al., 2009]. However, the effect of TIA without obvious infarct lesion on brain MRI on ARHI is still unknown in humans. Therefore, we aim to address this issue in this study. We hypothesized that TIA without obvious infarct lesion could contribute to hearing degeneration in older subjects.

Patients and Methods

Patients

From August 2007 to December 2009, 78 patients who were >50 years of age, who had at least one episode of TIA without obvious infarct lesion on brain MRI with and without diffusion-weighted imaging and who received pure tone audiometry in the Buddhist Dalin Tzu Chi General Hospital were included in this study.

The exclusion criteria were: age <50 years, conductive hearing loss, early-onset hearing impairment before 40 years of age, asymmetric sensorineural hearing loss (defined as a ≥ 15 dB hearing level (HL) asymmetry in two or more frequencies) [Cueva, 2004], cognitive dysfunction that prevents the patient from following the order of the audiometric exam, stroke, infarct or hemorrhagic lesion on brain MRI with and without diffusion-weighted imaging, pregnancy, hormone replacement therapy, and a history of any of the following: otitis media, acoustic trauma or exposure to high environmental noise (presented with a 4-kHz dip on audiogram), obvious ototoxic drugs exposure, any psychiatric disease, Ménière's disease, vestibular neuritis, labyrinthitis, labyrinthine fistula, benign paroxysmal positional vertigo, brain tumor or vestibular schwannoma, diabetes mellitus, chronic hepatitis, liver cirrhosis, chronic kidney disease, cancer, and radiation exposure.

We also selected the non-TIA group of 869 subjects randomly from the outpatient department at the same period by chart records. The subjects in the non-TIA group met all of the inclusion and exclusion criteria but were free of TIA.

Fig. 1. The 8 audiogram patterns classified by cluster analysis. For easy comparison, all patterns were calibrated at the 0.25 frequency. The patterns were named as follows: pattern 1 = severe 8-kHz dip; pattern 2 = peaked 8-kHz dip; pattern 3 = moderate 8-kHz dip; pattern 4 = abrupt loss; pattern 5 = moderate sloping; pattern 6 = mild sloping; pattern 7 = profound abrupt loss; pattern 8 = mild 8-kHz dip.

Definitions of TIA, Coronary Artery Disease, and HTN

The TIA patients were diagnosed by neurologists in our hospital based on the clinical symptoms and brain MRI. Patients who had at least one episode of any of the following symptoms were defined as TIA cases: temporary loss (<24 h) of vision, difficulty in speaking, weakness on one side of the body, numbness or tingling, dizziness or vertigo without obvious etiology [Sylaja and Hill, 2009; Tyrrell et al., 2010]. TIA cases with concurrent or subsequent infarct or hemorrhagic lesion on brain MRI were excluded from this study.

Coronary artery disease (CAD) was defined as a history of angina pectoris or confirmed by exercise electrocardiography (early onset angina, ST-segment depression ≥ 2 mm, ST-segment elevation, failure to increase systolic blood pressure or a sustained decrease in blood pressure after an appropriate rise during exercise, and low exercise tolerance) [Gibbons et al., 2003] or positive treadmill exercise test, positive coronary angiography or positive myocardial infarct study. HTN was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg [Carretero and Oparil, 2000].

Hearing Thresholds

There were 6 frequencies tested in routine pure tone audiometry. An average threshold of 250 and 500 Hz in both ears was defined as the average pure tone hearing level at low frequencies (PTA-low), an average threshold of 1 and 2 kHz in both ears as the average pure tone hearing level at middle frequencies (PTA-mid), and an average threshold of 4 and 8 kHz in both ears as the average pure tone hearing level at high frequencies (PTA-high).

Audiometric Configurations

To reduce the errors based on personal experiences and develop a consistency across clinics, we employed K-means cluster analysis to categorize the audiometric shapes [Lee et al., 2010]. Briefly, we treated the 6 frequencies in the audiogram as 6 metric variables in cluster analysis and calibrated them to the differences to a frequency of 250 Hz (the threshold at 250 Hz was regarded as 0 dB). Then, the K-means cluster analysis was employed to categorize the audiogram patterns. Eight audiogram shapes were identified for this study: severe 8-kHz dip (pattern 1), peaked 8-kHz dip (pattern 2), moderate 8-kHz dip (pattern 3), abrupt loss (pattern 4), moderate sloping (pattern 5), mild sloping (pattern 6), profound abrupt loss (pattern 7), and mild 8-kHz dip (pattern 8) (fig. 1).

Table 1. Basic characteristics for all participants and both non-TIA and TIA groups

Variables	All	Non-TIA group	TIA group	p value ¹
Age (means ± SD)	62.9 ± 9.2	62.4 ± 8.9	71.8 ± 10.2	<0.0001
Gender (female/male)	555/392	529/362	26/30	0.0565
HTN (no/yes)	661/286	655/236	6/50	<0.0001
CAD (no/yes)	822/125	792/99	30/26	<0.0001
Hearing thresholds (means ± SD)				
PTA-low	25.7 ± 19.4	25.0 ± 18.8	38.2 ± 23.3	<0.0001
PTA-mid	28.4 ± 21.3	27.4 ± 20.7	44.3 ± 23.5	<0.0001
PTA-high	43.3 ± 26.2	41.8 ± 25.9	66.4 ± 18.8	<0.0001

¹ p value for comparisons between non-TIA and TIA groups by Student's t test or χ^2 test.

Statistical Analysis

The data are presented as means ± standard deviations (SD) unless indicated otherwise.

Student's t test or χ^2 test was used to test the differences in variables between groups. A univariate and multivariate linear regression model using the least squares approach was performed to test the effect of TIA on PTA-low, PTA-mid, or PTA-high. The distribution of audiogram patterns was compared between the non-TIA group and the TIA group after adjusting for age, sex, and pure tone average of all frequencies. Multinomial logistic regression analysis was performed to examine the likelihood ratio of the audiogram patterns based on TIA with adjustment of age, sex, and mean hearing level of all frequencies.

p values <0.05 were considered statistically significant. All analyses were performed using STATA 10.0 software (Stata Corp LP, College Station, Tex., USA).

Results

Table 1 shows the characteristics of all participants in this study. The mean age was 62.9 ± 9.2 years for all 947 subjects; it was significantly higher in the TIA group than in the non-TIA group. The female-to-male ratio was higher in the non-TIA group than in the TIA group, whereas HTN and CAD were more prevalent in the TIA group than in the non-TIA group (table 1). As for hearing thresholds, the TIA group had poorer hearing function compared to the non-TIA group at all frequencies before adjusting for other variables.

Univariate linear regression analysis showed that age, male gender, TIA, HTN, and CAD had a significantly positive association with hearing thresholds at all frequencies (data not shown). TIA was significantly associated with HTN and/or CAD by univariate or multivariate linear regression analysis ($p < 0.001$, data not shown). That is, patients with TIA commonly also had preexisting HTN and CAD. Therefore, we could put only TIA, but not HTN and/or CAD, in the linear regression model for hearing dysfunction analysis first. By doing so, we found that TIA did not show a significantly positive association with PTA-low [β coefficient (β) ± standard error (SE) = 2.98 ± 2.33, $p = 0.202$]. However, TIA showed a positive association with PTA-mid of borderline significance (β ± SE = 4.51 ± 2.44, $p = 0.065$) and a significantly positive association with PTA-high (β ± SE = 8.63 ± 2.81, $p = 0.002$) after adjusting for age and sex (table 2).

When we considered HTN and/or CAD additionally in the multivariate linear regression analysis, TIA still showed a significantly positive association with PTA-high after adjusting for HTN, CAD, or both (table 3). However, TIA did not show a significant association

Table 2. Multivariate linear regression analysis for PTA-low, PTA-mid, or PTA-high according to age, gender, and TIA

	PTA-low	PTA-mid	PTA-high
Age	1.07 ± 0.06 (<0.001)	1.25 ± 0.06 (<0.001)	1.51 ± 0.07 (<0.001)
Gender (male vs. female)	1.94 ± 1.10 (0.077)	5.55 ± 1.15 (<0.001)	14.60 ± 1.32 (<0.001)
TIA	2.98 ± 2.33 (0.020)	4.51 ± 2.44 (0.065)	8.63 ± 2.81 (0.002)
Values are $\beta \pm SE$ with p values in parentheses.			

Table 3. Multivariate linear regression analysis for PTA-high by age, gender, TIA, HTN and/or CAD

	PTA-high	PTA-high	PTA-high
Age	1.47 ± 0.07 (<0.001)	1.48 ± 0.07 (<0.001)	1.46 ± 0.07 (<0.001)
Gender (male vs. female)	14.57 ± 1.32 (<0.001)	14.68 ± 1.32 (<0.001)	14.64 ± 1.32 (<0.001)
TIA	6.94 ± 2.92 (0.018)	7.50 ± 2.87 (0.009)	6.26 ± 2.95 (0.034)
HTN	3.20 ± 1.52 (0.035)	–	2.73 ± 1.55 (0.077)
CAD	–	3.84 ± 1.99 (0.054)	3.14 ± 2.03 (0.122)
Values are $\beta \pm SE$ with p values in parentheses.			

Table 4. Multinomial logistic regression for audiogram patterns by TIA after adjusting for age, gender, and mean hearing level of all frequencies

Patterns	β	SE	95% CI	p value
1 (severe 8-kHz dip)	1.07	0.60	–0.09~2.23	0.071
2 (peaked 8-kHz dip)	–11.5	1,995.72	–3,923.02~3,900.06	0.995
3 (moderate 8-kHz dip)	1.70	0.78	0.17~3.24	0.029
4 (abrupt loss)	0.73	0.62	–0.48~1.95	0.235
5 (moderate sloping)	–0.002	0.916	–1.80~1.79	0.998
6 (mild sloping)	base outcome ¹	–	–	–
7 (profound abrupt loss)	0.60	0.60	–0.58~1.78	0.316
8 (mild 8-kHz dip)	1.13	0.67	–0.20~2.45	0.095

CI = Confidence interval. ¹ Pattern 6 was chosen as a base category or as the comparison group in the model.

with PTA-low or PTA-mid after additionally adjusting for HTN, CAD or both diseases (data not shown). Furthermore, subgroup analysis by sex showed that TIA only showed a significantly positive association with PTA-high ($\beta \pm SE = 9.79 \pm 3.88$, $p = 0.012$) in female subjects, but not in males ($\beta \pm SE = 7.45 \pm 4.15$, $p = 0.073$). Therefore, TIA was an independent risk factor for ARHI, especially in the high frequencies and in females.

Table 4 shows the results of multinomial logistic regression for audiogram patterns by TIA after adjusting for age, sex, and mean hearing level of all frequencies. Pattern 3 (moderate 8-kHz dip; $\beta \pm SE = 1.70 \pm 0.78$, $p = 0.029$) was significantly more prevalent in the TIA

group than in the non-TIA group, whereas patterns 8 (mild 8-kHz dip; $\beta \pm SE = 1.13 \pm 0.67$, $p = 0.095$) and 1 (severe 8-kHz dip; $\beta \pm SE = 1.07 \pm 0.60$, $p = 0.071$) were slightly more prevalent in the TIA group. These findings were compatible with the results based on the frequency analysis.

Discussion

This study provides new insight into the characteristics of hearing impairment in patients with TIA. We found that the presence of TIA shows a significant association with PTA-mid and PTA-high in adults. Similarly, audiometric configuration analysis also revealed that the moderate 8-kHz dip pattern had a higher likelihood ratio for TIA patients. Both analyses suggested that TIA was associated with ARHI, especially in the mid to high frequencies.

Previous studies found that HTN, MI, and other CVD were associated with ARHI, especially in older women [Torre et al., 2005; Rosenhall and Sundh, 2006; Agrawal et al., 2009; Friedland et al., 2009]. It was shown that the incidence of heart disease among women rapidly approaches that in men [Lee and Foody, 2008], and women lose the protective effect of estrogen on hearing after menopause [Tandon et al., 2001; Thompson et al., 2006; Hwang et al., 2008]. Therefore, it is reasonable to expect that the hearing of women could be more obviously affected by CVD. The results of this study support the presence of gender differences in auditory dysfunction [Torre et al., 2005; Rosenhall and Sundh, 2006; Agrawal et al., 2009; Friedland et al., 2009].

The short-term effects of TIA on hearing dysfunction have been reported before, for example TIA-related hearing disorders were proven to be reversible [Drake, 1990; Hülse, 1994] or unilateral [Yamasoba et al., 2001; Lee and Baloh, 2005; Lee et al., 2009]. The wave V of ABRs was significantly longer in latency and lower in amplitude in cervical vertigo, even though hearing was not impaired [Drake, 1990; Hülse, 1994]. Mills and Ryals [1985] also found that hearing disorder was reported subjectively by 15% of patients, whereas threshold shifts of 5–25 dB in low frequencies were noted objectively by 40% of patients during vertigo attack. In addition, the mean absolute latency of wave V of ABRs was significantly longer in the group with decreased anterior (carotid) or posterior (vertebrobasilar) circulation than in the matched control group in middle-aged males. Now, our study illustrates that TIA without ischemic lesion might exert a longer effect on auditory dysfunction and contribute to ARHI.

Although the issue of which structures (i.e. cochlea or vestibule) are more sensitive to ischemia in humans is still unclear, the inner ear is certainly sensitive to ischemia because it requires high-energy metabolism and the labyrinthine artery is an end artery with minimal collaterals from the otic capsule. It is generally assumed that direct evidence of blood flow disturbance in the cochlea is a main cause of acute hearing loss of a vascular cause in patients with anterior inferior cerebellar artery infarction. Also the apical cochlear is particularly vulnerable (reflected as low-frequency hearing loss) to ischemia [Nakashima et al., 2003]. On the other hand, cochlear ischemia could also lead to a reduction of the endocochlear potential [Ohlemiller et al., 2006], which could affect all turns of the cochlea. Thus, the observation that CVD is associated with middle- and high-frequency loss is also reasonable. However, it is still unknown which mechanisms are dominant or which frequencies would be affected first and which later as CVD deteriorates.

The findings from animal studies might reveal partially the susceptible frequencies of TIA-related auditory dysfunction. Sporadic fusion of hair cells and the disappearance of hair cell stereocilia did not begin until 4 days after transient ischemia in gerbils. On subsequent days, the loss of hair cells, especially inner hair cells (IHCs), and the degeneration of spiral

ganglion neurons became apparent. Ten days after ischemia, the mean percentage cell loss of IHCs was 6.4% in the basal turn, 6.4% in the second turn, and 0.8% in the apical turn, and the number of SGC neurons had decreased to 89% of pre-ischemic status [Koga et al., 2003]. Interruption of the blood supply to the cochlea of gerbils for 15 min caused a remarkable elevation of the compound action potential threshold. The compound action potential threshold recovered to some extent with reperfusion, but not to pre-ischemic levels [Hyodo et al., 2001]. Interestingly, sublethal ischemia prevented lethal ischemia-induced hair cell degeneration and ameliorated hearing impairment [Takeda et al., 2009]. Although data are still limited, it seems that the short-term effect of TIA might be harmful for the high frequencies of hearing according to the results of our human study. However, the long-term effect of TIA on the susceptible frequencies of hearing still needs to be evaluated by more studies in the future.

Conclusions

TIA without obvious infarct lesion on brain MRI could contribute to hearing degeneration in aged subjects, especially in the high frequencies and in females, according to frequency analysis. Audiometric configuration analysis also supported these findings.

Disclosure Statement

There are no conflicts of interest.

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