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Plasma Glial Cell-Derived Neurotrophic Factor and Insulin-like Growth Factor-1 Levels Were Not Correlated with the Severity of Age-Related Hearing Impairment in Humans

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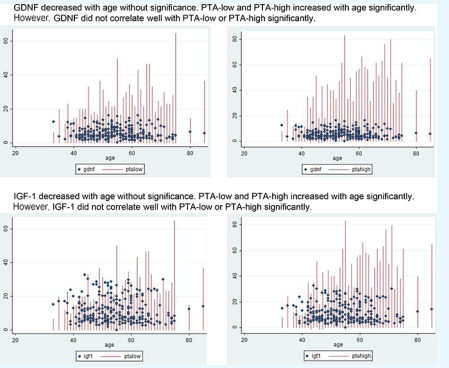
ABSTRACT: The relationship between plasma glial cell-derived neurotrophic factor (GDNF) or insulin-like growth factor-1 (IGF-1) levels and age-related hearing impairment (ARHI) has not been reported in humans. By cross-sectional design, 268 subjects older than 33, with normal cognitive function and normal or symmetric sensorineural hearing loss, were selected randomly. Multivariate linear regression analysis was performed to test the impact of the plasma GDNF or IGF-1 level on the pure tone threshold of low frequencies (PTA-low) and high frequencies (PTA-high), respectively. Results showed that plasma GDNF and IGF-1 levels decreased with age without statistical significance. Multivariate linear regression analysis showed that GDNF or IGF-1 levels were not significantly correlated with PTA-low or PTA-high after adjusting age, gender, body mass index, systemic diseases, habits, and noise exposure. In conclusion, plasma GDNF or IGF-1 levels were not associated with the severity of ARHI in humans. However, these findings did not support the roles of GDNF or IGF-1 genotypes on hearing.



INTRODUCTION

Age-related hearing impairment (ARHI) is a common sensory disorder in middle-age adults and the elderly. Many factors would contribute to ARHI, for example, genetic polymorphisms, obesity, metabolic syndrome, obstructive sleep apnea, noise, hormone replacement therapy, bad habits, ototoxic compounds, and lower socioeconomic status.[1−3] Oxidative stress damage was the most important underlying mechanism for ARHI.[4] Also, our previous study found that plasma reactive oxygen species levels were positively associated with the severity of ARHI in humans,[5] even though there were still other hypotheses accounting for ARHI.

Glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) play key roles in the early development of the central auditory pathway and the inner ear. Also, these neurotrophic factors are responsible for the maintenance of auditory neurons and protect against acoustic trauma or ototoxicity.[6] GDNF expression was strongly upregulated in the auditory nerve following deafness, indicating their importance in protecting the auditory nerve against cell damage.[7] However, no significant changes in the expression of GDNF family genes were found in the inferior colliculus following deafness.[7] Neurotrophic factors other than neurotrophin-3 (NT-3) are available to spiral ganglions (SGN) even as they are dying after deafening.[8] It seemed that these findings might conflict with the hypothesis that SGN death is attributable to a lack of neurotrophic factors. Furthermore, the correlation of tissue and/or blood neurotrophic factor levels and the severity of age-related hearing impairment (ARHI) were still unknown.

Insulin-like growth factor-I (IGF-I) plays a central role in embryonic development and adult nervous system homeostasis. IGF-I also regulated cochlear development, growth, and differentiation, and its mutations are associated with hearing loss in mice and men.[9,10] Human IGF-1 mutations cause profound deafness, poor growth, and mental retardation. Similarly, lgf1−/− mice are dwarfs with poor survival rates and congenital profound sensorineural deafness.[10,11] Decreased circulating IGF-1 level has been related to age-related cognitive and brain alterations in humans.[10] Also, IGF-1 serum levels decreased with aging and there are concomitant hearing loss and retinal degeneration in mice.[9] However, Riquelme et al.[10] found that age-related spiral ganglion (SGN) degeneration was not evident in the Igf1 null mice. Also, the exact correlation of

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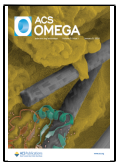

tissue and/or blood IGF-1 levels and the severity of ARHI were still not documented.

Previous animal and genetic studies suggested that GDNF and/or IGF-1 genotypes and/or serum protein levels were associated with hearing functions, especially for congenital hearing impairment. However, the actual relationship between the tissue or blood GDNF and/or IGF-1 levels and ARHI has not been reported in humans until now. For ethical reasons, it is very hard to get tissues or organ fluids for inner ear studies in humans. So, in this study, we aimed to investigate the relationship between plasma GDNF and IGF-1 levels and the severity of ARHI.

SUBJECTS AND METHODS

Subjects. From January 2009 to December 2009, 268 subjects older than 33, with normal cognitive function and normal or symmetric sensorineural hearing loss (SNHL), were selected randomly from the Dalin Tzu Chi Hospital, Chiayi, Taiwan. All subjects received cognitive function and medical history questionnaires, otoscopy, pure tone audiometry, and tympanogram. Exclusion criteria included age younger than 33, early onset hearing impairment, cognitive dysfunction, poor reading ability, middle ear diseases, conductive hearing loss (air-bone gap in the audiogram), asymmetric SNHL [defined as a 15 dB hearing level (dB HL) or greater asymmetry in two or more frequencies], acoustic trauma (3−6 k Hz dip in the audiogram), exposure to ototoxic drugs, pregnancy, women on hormone replacement therapy, major neurological or psychiatric disease, brain tumor, vertigo, liver cirrhosis, chronic kidney disease (CKD) under dialysis, cancer, head and neck radiation exposure, heavy smoker, abuser of alcohol, or controlled substances. The Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (B09702023-1) has proved this study. Informed written consent was waived because the study was a retrospective data analysis.

Medical History and Health-Related Habits. All participants were asked to answer all questions in a detailed questionnaire. Systemic diseases were treated with a regular regimen. Consumption of smoking and alcohol drinking by frequency (cigarettes or drinks, per month) plus duration (months) was graded as 1−5. Grade 1 was regarded as nonsmokers or nondrinkers, while grades 2−5 were regarded as smokers or drinkers. Noise exposure by frequency (days, per month) plus duration (months) was graded as 1−5. Grade 1 was regarded as no exposure, while grades 2−5 were regarded as exposure.

Morphometry. Height, body weight, and waist circumference (WC) were measured after an overnight fast. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). WC was measured in a horizontal plane, midway between the inferior margin of the ribs, and the superior border of the iliac crest. Central obesity in Asians is defined as WCs of >90 cm for males and >80 cm for females according to International Diabetes Federation guidelines.[12]

Pure Tone Audiometry. Sounds were delivered via earphone (Telephonics Corp., Farmingdale, NY) in a double-walled, soundproof booth. Six frequencies (250−8000 Hz) were tested in pure tone audiometry (GSI 61 Audiometer, VIASYS Healthcare, Hong Kong Ltd., Hong Kong). First, the mean threshold of each frequency was calculated for each subject in both ears. Then, mean thresholds of 250, 500, and 1 k Hz were averaged as the average pure tone hearing level of low frequencies (PTA-low), and those of 2, 4, and 8 k Hz were the average pure tone hearing levels of high frequencies (PTA-high).

Measurement of GDNF and IGF-1 Activities in Plasma. To determine the GDNF and IGF-1 activities in plasma, we sampled overnight fasting venous blood and isolated plasma by centrifugation at 3000*g* for 20 min at room temperature. The plasma was immediately stored at −70 °C for further measurement. GDNF and IGF-1 concentrations were measured by a Human GDNF Assay Kit (Sunred/catalog no. 201-12-0123) and a Human IGF1 Assay Kit (Sunred/catalog no. 201-12-0104). The prepared samples, standards, and antibodies labeled with an enzyme (Str-HRP-Conjugate Reagent) were reacted for 60 min at 37 °C and washed five times for 2 min. After washing, Chromogen solutions A and B were added and reacted for 10 min at 37 °C. The stop solution was added, and then, the OD value was measured within 10 min. Absorbance was recorded at 450 nm with a multi-well plate reader (Anthos Zenyth 3100 Microplate Multimode Detector, Salzburg, Austria). The quantity of the product as measured by the amount of 450 nm absorbance was directly proportional to the number of GDNF and IGF-1.

Statistical Analysis. The data were presented as means ± standard deviation (SD). Student's *t*-test or Chi-square test was used to test the difference of means of numerical variables or distributions of categorical variables, respectively. Multivariate linear regression analysis was performed to test the impact of the plasma GDNF or IGF-1 level on PTA-low and PTA-high, respectively. To test whether GDNF or IGF-1 is an intermediate variable between many clinical factors and ARHI, we first only adjusted the age and gender in the multivariate linear regression model. To test whether GDNF or IGF-1 is an independent risk factor for ARHI, we then adjusted all clinical risk factors in the multivariate linear regression model. *P* values <0.05 were considered statistically significant in the models. All analyses were performed using STATA 10.0 software (Stata Corp, L.P., College Station, TX).

RESULTS

There were 268 subjects (110 males and 158 females) included in this study. Table 1 shows the clinical characteristics of all subjects. The mean age was 54.3 ± 9.1 years old. Age did not differ significantly in both genders (54.7 ± 9.3 years old for males versus 53.7 ± 8.9 years old for females, Student's *t*-test, $p = 0.3782$). The mean BMIs were 25.1 ± 2.7 for males and 23.4 ± 2.6 for females. The proportions of central obesity were 44.9% in males and 73.6% in females. The mean plasma GNDF level was 5.7 ± 3.3 ng/mL, whereas the mean plasma IGF-1 level was 11.3 ± 7.2 ng/mL for all subjects. The mean PTA-low was 16.3 ± 8.9 dB HL, the mean PTA-high was 23.4 ± 16.6 dB HL, and the mean PTA-mid 4 tones was 20.8 ± 13.3 dB HL.

The plasma GDNF level was not significantly different between males and females (5.5 ± 3.1 versus 6.1 ± 3.5, $p = 0.1201$). The plasma GDNF level grossly decreased with age, but the correlation was not significant (GDNF = −0.008 age + 6.148, $p = 0.725$). Also, the plasma IGF-1 level was not significantly different between males and females (11.1 ± 7.0 versus 11.6 ± 7.5, $p = 0.5531$). The plasma IGF-1 level grossly

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Table 1. Clinical Characteristics of All 268 Subjects[a]

variables	mean ± SD or proportion (%)
age (years old)	54.3 ± 9.1
gender (males)	59.0
BMI (kg/m^2)	24.4 ± 2.8
males	25.1 ± 2.7
females	23.4 ± 2.6
central obesity	
males (waist >90 cm)	44.9 (71/158)
females (waist >80 cm)	73.6 (81/110)
CAD	4.1 (11/268)
HTN	15.3 (41/268)
DM	5.2 (14/268)
dyslipidemia	1.5 (4/268)
CKD	0 (0/268)
smoking	14.5 (40/268)
drinking	22.4 (60/268)
noise exposure	12.7 (34/268)
GDNF	5.7 ± 3.3
IGF-1	11.3 ± 7.2
hearing thresholds	
PTA-low	16.3 ± 8.9
PTA-high	23.4 ± 16.6

[a]Abbreviation: SD, standard deviation; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; PTA-low, pure tone average of low frequencies; PTA-high, pure tone average of high frequencies.

decreased with age, but the correlation was not significant (IGF-1 = −0.038 age + 13.377, p = 0.430).

Tables 2 and 3 show the effects of GDNF on PTA-low or PTA-high separately by multivariate linear regression analysis.

Table 2. Multivariate Linear Regression Analysis for PTA-low or PTA-high by GDNF, Age, and Gender[a]

β ± SE (P value)	PTA-low	PTA-high
GDNF	0.081 ± 0.151 (0.591)	0.138 ± 0.253 (0.586)
age	0.397 ± 0.055 (<0.001)	1.006 ± 0. 092 (<0.001)
gender	−0.563 ± 1.016 (0.580)	0.138 ± 0.253 (0.006)

[a]Abbreviations: β = coefficient; SE, standard error.

Table 3. Multivariate Linear Regression Analysis for PTA-low or PTA-high by GDNF, Age, Gender, BMI, Systemic Diseases, and Habits[a]

β ± SE (P value)	PTA-low	PTA-high
GDNF	0.102 ± 0.155 (0.510)	0.147 ± 0.258 (0.569)
age	0.357 ± 0.059 (<0.001)	1.008 ± 0.098 (<0.001)
gender	−0.687 ± 1.139 (0.547)	3.705 ± 1.901 (0.052)
BMI	0.083 ± 1.192 (0.668)	0.765 ± 0.321 (0.018)
CAD	2.672 ± 2.596 (0.304)	1.799 ± 4.335 (0.678)
HTN	0.752 ± 1.604 (0.640)	−1.980 ± 2.677 (0.460)
DM	4.833 ± 2.390 (0.044)	3.910 ± 3.990 (0.328)
dyslipidemia	−1.182 ± 4.196 (0.778)	0.587 ± 7.006 (0.933)
CKD	dropped	dropped
smoking	−0.242 ± 0.419 (0.564)	0.376 ± 0.699 (0.591)
drinking	−0.353 ± 0.510 (0.489)	−0.255 ± 0.851 (0.765)
noise exposure	0.396 ± 0.465 (0.395)	0.989 ± 0.776 (0.204)

[a]Abbreviations: β = coefficient; SE, standard error.

In Table 2, GDNF was not significantly related to PTA-low (0.081 ± 0.151, p = 0.591) or PTA-high (0.138 ± 0.253, p = 0.586) after adjustment of age and gender. In Table 3, GDNF was not significantly related to PTA-low (0.102 ± 0.155, p = 0.510) or PTA-high (0.147 ± 0.258, p = 0.569) after adjustment of age, gender, BMI, CAD, HTN, DM, dyslipidemia, CKD, smoking, drinking, and noise exposure. These results suggested that the plasma GDNF level was not related to hearing thresholds in adults with ARHI.

Tables 4 and 5 show the effects of IGF-1 on PTA-low or PTA-high separately by multivariate linear regression analysis.

Table 4. Multivariate Linear Regression Analysis for PTA-low or PTA-high by IGF-1, Age, and Gender[a]

β ± SE (P value)	PTA-low	PTA-high
IGF-1	0.004 ± 0.070 (0.951)	0.045 ± 0.117 (0.697)
age	0.397 ± 0.055 (<0.001)	1.005 ± 0.092 (<0.001)
gender	−0.628 ± 1.015 (0.537)	4.655 ± 1.700 (0.007)

[a]Abbreviations: β = coefficient; SE, standard error.

Table 5. Multivariate Linear Regression Analysis for PTA-low or PTA-high by IGF-1, Age, Gender, BMI, Systemic Diseases, and Habits[a]

β ± SE (P value)	PTA-low	PTA-high
IGF-1	0.022 ± 0.071 (0.752)	0.037 ± 0.118 (0.754)
age	0.357 ± 0.059 (<0.001)	1.007 ± 0.099 (<0.001)
gender	−0.767 ± 1.145 (0.503)	3.680 ± 1.911 (0.055)
BMI	0.079 ± 0.193 (0.684)	0.745 ± 0.322 (0.021)
CAD	2.621 ± 2.601 (0.314)	1.684 ± 4.341 (0.698)
HTN	0.803 ± 1.607 (0.618)	−1.917 ± 2.682 (0.475)
DM	4.895 ± 2.395 (0.042)	4.007 ± 3.998 (0.317)
dyslipidemia	−1.289 ± 4.204 (0.759)	0.372 ± 7.019 (0.958)
CKD	dropped	dropped
smoking	−0.246 ± 0.420 (0.558)	0.361 ± 0.701 (0.607)
drinking	−0.325 ± 0.511 (0.526)	−0.237 ± 0.854 (0.781)
noise exposure	0.397 ± 0.466 (0.396)	0.987 ± 0.778 (0.206)

[a]Abbreviations: β = coefficient; SE, standard error.

In Table 4, IGF-1 was not significantly related to PTA-low (0.004 ± 0.070, p = 0.951) or PTA-high (0.045 ± 0.117, p = 0.697) after adjustment of age and gender. In Table 5, IGF-1 was not significantly related to PTA-low (0.022 ± 0.071, p = 0.752) or PTA-high (0.037 ± 0.118, p = 0.754) after adjustment of age, gender, BMI, CAD, HTN, DM, dyslipidemia, CKD, smoking, drinking, and noise exposure. These results suggested that the plasma IGF-1 level was not related to hearing thresholds in adults with ARHI.

In addition, subgroup analysis by gender showed that plasma GDNF and IGF-1 levels were not related to PTA-low or PTA-high significantly in males or females, respectively. That is, there were no gender differences in GDNF or IGF-1 and PTA scores.

DISCUSSION

This cross-sectional human study demonstrated no association between plasma GDNF and/or IGF-1 concentrations and peripheral hearing thresholds in adults and the elderly. To our knowledge, this is the first paper to investigate the relationship between GDNF and IGF-1 levels and ARHI in humans, although the association of the serum IGF-1 level and ARHI or age-related retinal degeneration in mice was studied before.[9]

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The evidence in this study did not support GDNF and/or IGF-1 hypothesis for ARHI in humans but did not support the roles of GDNF and/or IGF-1 genotypes on the early onset and late onset congenital hearing losses in animals and humans.

Previous studies showed that GDNF and BDNF were involved in the early development of the central auditory pathway and the inner ear.[6,9,10,13] Also, some studies claimed that these neurotrophic factors were associated with the maintenance of auditory functions during aging.[9,13] Also, IGF-1 receptors are expressed in the developing inner ear and the postnatal cochlear and vestibular ganglia.[11] In the inner ear, IGF-1 regulated the cell cycle and metabolism actions via intracellular signaling networks, RAF, AKT, and p38 MAPK protein kinases.[9] Mice lacking IGF-1 had increased auditory thresholds at early postnatal ages in mice and humans.[11] In the Igf1 null mouse, hearing loss is due to neuronal loss, poor innervation of the sensory hair cells, and age-related stria vascularis alterations.[9] In addition, IGF-1 serum levels decreased with aging and there are concomitant hearing loss and retinal degeneration in the mice.[9] However, IGF-1 deficiency did not lead to morphologic changes in the vestibular organ.[14]

However, there were still some reports against the roles of GDNF, BDNF, and/or IGF-1 in the auditory function. For example, increased GDNF expression in the auditory nerve was found in response to insult of deafness.[7] Expression of GDNF family genes did not alter in the inferior colliculus following deafness.[7] Neurotrophic factors other than NT-3 are present in the SG, even though the SGNs were lost in deafened rats.[8] SG degeneration was not obvious in the Igf1 null mice.[10] The expressions of the IGFs mRNA and protein were significantly increased in the cochlea of mice, mainly focused in the stria vascularis, with salicylate ototoxicity.[15] So, it seemed that these contradictory findings were shown and explained in quite different situations about congenital hearing loss, acquired acoustic trauma or ototoxicity, and the aging process. There is no doubt that genetic defects of neurotrophic factors or IGF-1 would have phenotypes of decreased levels of these proteins and congenital hearing loss. However, expression of some neurotrophic factors would increase transiently in some regions of the auditory system in response to insult on hearing. In the aging process, however, the association between neurotrophic factors and/or IGF-1 and auditory function was still inconclusive, especially for human beings. Now, our results suggest that plasma GDNF and IGF-1 have no contribution to ARHI in humans.

Although the endogenous GDNF and/or IGF-1 levels were not related to the severity of ARHI in humans, supplementation of exogenous GDNF and/or IGF-1 might be helpful for prevention of hearing loss or degeneration. For example, neurotrophic factors could protect against acoustic trauma or ototoxicity.[6] Shoji et al.[16] reported that NT-3, but not BDNF, could prevent noise-induced hearing loss. rhIGF-1 could treat poor linear growth and certain neurodegenerative diseases.[9] In addition, IGF-1 maintains the hair cell number of postnatal mammalian cochlea after various kinds of ototoxicity, noise exposure, and ischemia in animals and improves hearing in patients with sudden sensorineural hearing loss.[17−19] In such situations, IGF-1 could inhibit hair cell apoptosis via activation of both the PI3K/Akt and MEK/ERK pathways and increase the proliferation of supporting cells via increasing Netrin1 expression and activating the MEK/ERK pathway.[18−20]

However, some limitations of this study might weaken our results. For example, as we know, it is impossible to obtain inner ear fluid in live human beings ethically. We could provide evidence that only plasma GDNF and IGF-1 may not be associated with ARHI in humans. However, we still cannot claim undoubtedly that GDNF and/or IGF-1 were not related to ARHI in humans because the correlation between plasma GDNF and/or IGF-1 and inner ear GDNF and/or IGF-1 was never documented until now.

CONCLUSIONS

This cross-sectional study showed that the plasma GDNF and/or IGF-1 concentrations were not related to ARHI in humans. However, our findings did not protect against the effects of GDNF and/or IGF-1 genotypes on congenital hearing loss in animals and humans. We suggested that more large-scale studies with more patients should be conducted to assess this issue in the future.

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Author Contributions

[▽]P.-S.H., S.-R.W., and S.-W.H. contributed to this article equally. Conceptualization, resources, and writing − original draft preparation and review and editing, J.-H.H.; methodology, J.-H.H. and P.-S.H.; software, P.-S.H.; validation and data curation, P.-S.H., S.-R.H., and S.-W.H.; formal analysis and investigation, S.-R.H. and S.-W.H. All authors have read and agreed to the published version of the manuscript.

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Notes

The authors declare no competing financial interest.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (B09702023-1). Informed written consent was waived because the study was a retrospective data analysis.

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