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SERUM BIOMARKERS AND NOISE-INDUCED HEARING LOSS.

SOLIMAN ABDELATIF
ENT DEPARTMENT, FACULTY OF MEDICINE, ALAZHAR UNIVERSITY., daktarbay050877@gmail.com

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Serum Prestin and Otolin-1 Levels as Biomarkers of Noise-Induced Hearing Loss

Soliman S. Abdelatif Ghanem[1,*] MD.

** Corresponding Author:*
Soliman S. Abdelatif Ghanem
Daktarbay050877@gmail.com

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[1]*Department of ENT, Faculty of Medicine, Al-Azhar University, New Damitta, Egypt.*

ABSTRACT

Background: Serum biomarkers are used in the field of medicine since many years. One of the most important advantage of the biomarkers as its considered objective tests and it can be used as an indicator for many health conditions not only normal, pathological (diagnosis & prognosis) but also to show the effect of treatment.
In fact, there is special biomarkers (prestin & Otolin-1) playing an important role in the audio-vestibular functions of the inner ear. Many of the studies have reported that there is a relationship between the levels of these biomarkers and hearing disorders.
Aim of the work: The aim of this study is to search the relationship between serum biomarkers such as serum Prestin and Otolin-1 levels and noise-induced hearing loss (NIHL).
Patients and Methods: This study was conducted among 100 NIHL patients; 66 males and 34 females, and 50 healthy subjects; 30 males and 20 females served as controls with normal hearing threshold. Pure tone audiometry (PTA) and assessment of serum level of both prestin and otolin -1 were done for all participants.
Result: Air and bone conduction threshold showed significant decrease in NIHL group than controls (P <0.05). Serum Prestin and Otolin-1 levels were significantly elevated in NIHL group than in controls (P <0.05). Both tests showed high accuracy levels (86% and 92%, respectively).
Conclusion: Based on the results of this study, serum prestin and otolin-1 could be used in early detection of hearing loss in individuals at high risk of noise exposure.

Keywords: *Noise induced; Hearing loss; Air conduction; Prestin biomarkers.*

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INTRODUCTION

Noise-induced hearing loss (NIHL) is the most common form of sensori-neural hearing loss caused by exposure to noise. Exposure to high intensity sound (noise) affects the outer hair cell plasma membrane liquidity [1].

Sensori-neural hearing loss (SNHL) is the commonest type of hearing loss due to damage of hair cells (receptor of hearing), degeneration of neurons & or neuron-hair cell junction [2]. The most common causes of SNHL are degenerative changes associated with age, noise exposure, drugs that have ototoxic effect & rarely due to genetic changes [3].

It is known that around 1.2 billion cases of hearing disorders are due to exposure to high intensity sound worldwide [4]. Exposure to high intensity sound levels for long duration, is the cause of about 16% of cases of hearing loss in adults worldwide [4,5&6].

Exposure to high intensity sound leads to irreversible damage of hair cells by multiple pathological mechanisms. The hair like projection (stereocilia) on hair cells surface are easily damaged by mechanical trauma caused by the high intensity sound, directly affecting the cellular organization of the organ of Corti. Also, the severe and profound types of hearing loss is not only due to mechanical effect of high intensity sound; but also due to other factors such as increase of the free radicals that affect the growth of hair cells [2].

The affecting mechanisms primarily involves the contraction of outer hair cells, derived by changes in potential membrane and mediated by prestin [7].

Prestin, is a protein in the outer hair cells (OHCs) that is responsible for good electro-motility of the cells and so, any changes in the level of the prestin can affect the electro-motility of the hair cells and lead to hearing disorders [8].

Prestin is an essential protein required for good functioning of the inner ear as the noise induced restricted expression of it results in hearing loss. A molecular targeted delivery of polymersomes mediated drug (prestin) in OHC with some degree of

hearing loss has led to complete cure or at least some improvement of the hearing disorder [9, 10&11].

Otolin-1 is a glycoprotein specifically secreted in the inner ear [12]. Its mRNA expression is restricted to the vestibular part of the inner ear, in addition to stria vascularis of organ of Corti [13]. It interacts with prestin to improve the function of the inner ear. Therefore, these two protein can possibly be used as circulatory biomarkers special for NIHL [14].

The aim of this study is to investigate the relationship between serum Prestin and Otolin-1 levels and noise-induced hearing loss.

PATIENTS AND METHODS

This cross-sectional study was conducted on one hundred (100) patients with NIHL representing the study group. Another fifty (50) normal healthy adult subjects were selected from relatives accompanying patients representing the control group. The age of both groups ranged from (20-40) years and represented both genders. All patients and controls were recruited from Damietta, Al-Azhar University Hospital, Egypt from May 2018 to December 2020.

This study was approved by the local ethics and research committee of Al-Azhar Faculty of Medicine in New Damietta. An informed consent was taken from all patients before starting the study.

For the control group, the inclusion criteria was the normal otoscopic finding, normal hearing threshold and normal middle ear functions as evidenced by tympanometry and acoustic reflex with no history of ear diseases nor any history of medical systemic diseases such as any rheumatic diseases, diabetes mellitus, hypertension, smoking, renal and cardiovascular diseases. The patients group have the same criteria of the control group except that they are having
a history of noise exposure and/or mobile phone users for more than one hour/day.

Instrumentation:

Sound treated room locally made according to international specifications.

One channel intracoustic audiometer GSI (model AD229b), calibrated according to ANSI standards.

Impedance-meter Interacoustics (model AT235).

Methods:

All individuals participated were subjected to the following:

Full history taken to exclude systemic diseases, noise exposure, ototoxic drug intake, and family history of hearing impairment.

Otological examination.

Basic audiological evaluation, which included the following:

Pure tone audiometry from (250 – 8000 Hz) for air conduction, from (500 – 4000 Hz) for bone conduction in octave steps. The air conduction stimulus was delivered via supra-aural headphone model TDH 39P. The bone conduction was delivered via bone conduction vibrator model B71.

Speech audiometry including:

Speech reception threshold (SRT) using Arabic spondee words.

Speech discrimination scores using phonetically Arab balanced words (PB words).

Impedancemetry included:

Tympanometry done at pressure range from (+200 to – 400 mm H_2O).

Acoustic reflex threshold elicited ipsilaterally and contralaterally using frequency range of (500 up to 4000Hz).

Laboratory tests for the assessment of blood prestin & otolin-1 levels were done by ELISA.

Statistical analysis

Statistical analyses were completed using SPSS v23 statistical software (SPSS, Inc, Chicago, Illinois). Descriptive statistics (means, standard deviations, frequencies, and correlation coefficients) were calculated for all measures. To compare between two groups, a paired t-test was carried out to determine P values using the Pearson's correlation test and a χ^2 test and a one-sample t-test and Wilcoxon test were performed when appropriate. In comparison between more than two groups (F) test by Analysis of Variance (ANOVA), p less than 0.05 was considered statistically significant.

RESULTS

The study included 100 NIHL patients (66 males and 34 females) representing the patients' group with the age ranging from 30 to 50 years (mean ± SD of 41.6 ± 6.12 years). The 50 apparently healthy subjects (30 males and 20 females) represent the control group with age ranging from 26 to 48 years (mean ± SD of 39.7 ± 5.93 years). The two groups were matched in sex and age (P >0.05) as well as smoking habit which was present in 68.0% of patients and 62% of controls as shown in table (1).

Measurement of air conduction hearing thresholds of both right and left ears shows significant decline in NIHL patients compared to control subjects. Bone conduction hearing thresholds of both right and left ears showed significant elevation in NIHL in patients compared to control subjects. Pure tone audiometry (PTA) showed a statistically significant decrease in NIHL compared to controls (P <0.05), Table (2). The level of noise exposure also showed statistically significant values (P <0.05) between the two groups as shown in Table (2).

The serum Otolin-1 and Prestin levels were significantly higher in NIHL group compared to control subjects (P <0.05) as shown in Table (3). Comparison between serum Otolin-1 and Prestin biomarkers regarding their accuracy showed highly significant values in detection of hearing loss as shown in Table (4).

	NIHL group N = 100		Control group N = 50		Test of significance	
Gender	No.	%	No.	%	χ^2	P
• **Males**	66	66.0	30	60.0	0.097	0.228
• **Females**	34	34.0	20	40.0	0.088	0.335
• **Total**	100	100	20	100		
Smoking	68	68.0	31	62	0.256	0.067
Age (years):	Mean	±SD	Mean	±SD	t-test	P
• **Mean ± SD**	41.6	6.12	39.7	5.93	0.0254	0.437
• **Range**	Min	Max	Min	Max		
	30	50	26	48		
Exposure duration (months)	15.8	6.34				
Exposure time (h/day)	8.65	3.21				

χ^2 = Chi square test, P >0.05= non-significant.

Table 1: Demographic characteristics of the studied groups.

Hearing threshold	NIHL group (Mean ± SD)	Control group (Mean ± SD)	Significance	
			T	P
Air conduction:				
• **Right ear (Hertz)**	3.12 ± 3.09	10.67 ± 6.18	0.642	0.004*
• **left ear (Hertz)**	3.69 ± 3.52	12.84 ± 6.41	0.815	0.002*
Bone conduction:				
• **Right ear (Hertz)**	3.48 ± 3.31	2.18 ± 2.57	0.424	0.007*
• **left ear (Hertz)**	3.69 ± 3.39	2.20 ± 2.69	0.397	0.006*
PTA (Hertz)	7.42 ± 2.38	11.27 ± 3.53	0.268	0.012*
Exposure level (db)	86.3 ± 7.19	45.2 ± 5.62	0.735	0.003*

* P <0.05= significant. PTA: pure tone audiometry, db: decibel.

Table 2: Tests of hearing function and exposure level in both groups.

Prestin (pg/ml)	NIHL group	Control group	T	P
Mean ± SD	166.88 ± 75.92	98.76 ± 53.67	0.741	0.001*
Range	85 – 199	51.6 – 125.7		
Otolin-1 (pg/ml)				
Mean ± SD	211.34 ± 85.54	72.62 ± 14.89	0.956	0.001*
Range	68.6 – 314.4	47.9 – 96.7		

* P <0.001= highly significant.

Table 3: Serum Prestin and Otolin-1 levels in both groups.

Test	Sensitivity	Specificity	Accuracy	AUC	P value
Prestin	91%	81%	86%	0.85	0.001*
Otolin-1	96%	86%	92%	0.90	0.001*

*P < 0.001 = highly significant.

Table 4: Comparison between serum Prestin and Otolin-1 biomarkers regarding their accuracy of hearing loss detection.

DISCUSSION

NIHL is a one of the common progressive SNHL caused by noise exposure. With the rapid development of industrialization, the risk of NIHL is increasing in people and has become a global public health problem [15].

WHO assessed that 10% of the worldwide population are exposed to noise contamination, with about 5.3% NIHL cases [16&17]. Biomarkers are significant and beneficial molecules for early diagnosis of several diseases and monitoring of the treatment period [12].

Pure tone audiometry showed a statistically significant decrease in NIHL compared to controls (P <0.05). The level of noise exposure also showed statistically significant values (P <0.05) between the two groups.

Measurement of serum Otolin-1 and Prestin levels showed significant elevation in NIHL group compared to control subjects (P <0.05). Comparison between serum Otolin-1 and Prestin biomarkers regarding their accuracy showed highly significant values in detection of hearing loss. It is a proof of the concept for a blood biomarker specific for inner ear noise-induced injury in human for the first time. Also, level of these biomarkers was increased independently with the duration of noise exposure.

This was in accordance with Hana and Bawi [1], who emphasized that after exposure to noise for certain duration, prestin and otolin-1 levels were significantly higher than that of control levels. But they stated that the current diagnostic tools remain limited in early detection of hearing loss.

Also, in agreement to these results Parham et al. [11,18&19] reported similar results. Doğan et al. [12] and Palva et al.[20], reported a significant association between duration of drilling sound after head surgery and hearing loss. Doğan et al.[12], reported elevation of Otolin-1 after these operations. Also, Tabtabai et al.[21],

demonstrated that Otolin-1 levels increase due to age-related demineralization. A drill is a frequently used instrument in ear surgeries [22].

Sun et al. [9], reported that prestin can be recognized and evaluated utilizing ELISA procedure in plasma of both patients with idiopathic sudden sensorineural hearing loss (ISSHL) and controls without history of hearing loss. But the normal concentration in ISSHL is much higher than those of controls.

The development of a serological marker will help in early detection of the condition, before the hearing is permanently affected by noise. Outer hair cell biomarker such as prestin and otolin-1, which can be measured within the blood, may serve as compelling markers surveying the cochlea against NIHL [1].

prestin concentrations in normal hearing individuals were detected because of the normal turnover (apoptosis) in the outer hair cells membrane [8]. The NIHL is related to increased prestin level in the OHCs. The prestin levels in residual cells decreases some weeks later. Consequently, prestin level changed after NIHL by time and so comparable changes in circulating prestin level may be identified [19].

Shortly after damage, OHCs undergo apoptosis, and prestin concentration is anticipated to raised, but as the apoptotic mechanisms halt, prestin concentrations drop reflecting a diminished number of surviving OHCs, so it can be used as a marker of hair cell damage. Otolin-1 in the serum of controls is normally found in otoconia and therefore, higher otolin-1 level may be a product of increased turnover with degeneration in NIHL patients. An ideal biomarker had to be tissue specific, detectable, and measurable [23&24].

Parham et al. [18], suggested that prestin might be considered a biomarker for OHC damage because of the following: First, prestin is markedly expressed in the lateral membrane of the OHCs. Second, after OHCs degeneration, prestin could be present in phagosomes of the supporting cells and ends in the circulation. Third, prestin size is 80kDa which is too small to pass the blood-labyrinthine barriers and entering the circulation. Finally, due to extreme sensitivity of ELISA, picogram quantities of prestin released into circulation can be identified [11]. OHCs damage is thought to be one of the important events that leads to hearing loss, especially in high-frequency[25].

CONCLUSION

Based on the results, serum prestin and otolin-1 can be used in identifying hearing loss in individuals at high risk of noise. They may be considered potential indicators for different types of hearing loss.

Expanded studies should be done on the same subject, with increasing the number of participants, addition of other biomarker investigation. Other types of hearing loss, should be included such as presbycuasis, sudden hearing loss, to approve or exclude the relationship between these biomarkers and different types of hearing loss.

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