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Original Article

Audiometric notch for the prediction of early occupational hearing loss and its association with the interleukin-1beta genotype

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الملخص

أهداف البحث: يعد فقدان السمع الناتج عن الضوضاء مشكلة صحية صناعية متكررة لا علاج لها. يمكن أن يمنع التشخيص المبكر لفقدان السمع الناتج عن الضوضاء تدهور السمع، خاصة في ترددات الكلام. وتهدف هذه الدراسة إلى تقييم ضعف السمع عند العمال المعرضين للضوضاء المهنية. كما تم تقييم الشقوق السمعية وتعدد الأنماط الجينية.

طرق البحث: شملت الدراسة ٩٨ عاملا يعملون في مصنع للنسيج. وتم إجراء مقياس السمع لطبقة الصوت الصافية لجميع العمال كما تم قياس مستوى الضوضاء في أربعة مواقع عمل مختلفة في قسم الغزل. وتم تحديد تعدد الأشكال الجيني. وتم إجراء الاختبارات السمعية باستخدام دليل تشخيص السمع لطبقة الصوت الصافية.

النتائج: أظهرت النتائج أن العمال تعرضوا لمتوسط مستوى الضوضاء قدره ١٠٥.٥٥ ديسيبل. يمثل العمال الذين يشكون من طنين الأذن ٢٧.٦ ٪ وعانى معظم العمال درجة من ضعف السمع في إحدى الأذنين، لكن لم يتجاوز أي منهم ٦٠ ديسيبل. وجدت الشقوق السمعية في إحدى الأذنين أو كليهما. لم تظهر الشقوق السمعية عند ٢٨.٦٪ من العمال فقط. كان النمط الجيني "ت ت"هو الأكثر شيوعا بين العمال بنسبة ٤٩ ٪، بينما كان "ت س" يمثل ٣٩.٨ ٪ و "س س" يمثل ١١.٢ ٪ من العمال. ارتبط النمط الجيني "س س" مع التدخين (٥٤.٥٪) وكذلك الشقوق السمعية (١٠٠ ٪). لم يظهر طنين الأذن اختلافا كبيرا في الأنماط الجينية.

الاستنتاجات: أظهرت الدراسة علاقة بين النمط الوراثي "س س" والتدخين، وكذلك الشقوق السمعية في العمال المعرضين للضوضاء المهنية. يجب متابعة العمال الذين يظهر لديهم شق سمعي بشكل منتظم. وهناك حاجة إلى مزيد من الدراسات لتأكيد وجود علاقة متبادلة بين الطنين، والشقوق السمعية والأنماط الجينية.

الكلمات المفتاحية: الشقوق السمعية؛ النمط الوراثي س س؛ والأنماط الجينية؛ الطنين؛ التدخين

Abstract

Objectives: Noise-induced hearing loss (NIHL) is a frequent and irreversible industrial-health problem, the early diagnosis of which can prevent hearing deterioration, especially of speech frequencies. This study aimed to assess hearing impairment in workers occupationally exposed to noise. Audiometric notches and IL-1β gene polymorphisms were evaluated.

Methods: The study included 98 workers employed in a textile factory. Pure-tone audiometric testing was conducted for all workers, using a manual pure-tone diagnostic audiometer, and the noise level was measured at four different work sites in a spinning section. IL-1β gene polymorphism was determined using PCR-RFLP methods.

Results: Workers were exposed to a mean noise level of 105.5 dB. As many as 27.6% of them complained of tinnitus and the majority suffered from some degree of hearing loss in either ear, but none of them exceeded 60 dB. Audiometric notches were detected in either one or both ears. Only 28.6% of workers showed the absence of notches. The TT genotype of IL-1β polymorphisms was dominant in 49% of the workers, whereas TC was predominant in 39.8% and CC in 11.2%. The CC genotype was associated with smoking (54.5%) and audiometric notches (100%). The IL-1β genotype distribution showed no significant difference with or without tinnitus.

Conclusion: This study showed an association between the CC genotype and smoking as well as audiometric notches in workers occupationally exposed to noise. Workers showing audiometric notches should be followed up regularly. Further studies are required to

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confirm the interrelationship amongst tinnitus, audiometric notches, and IL-1β genotypes.

Keywords: Audiometric notches; CC genotype; IL-1β genotypes; Smoking; Tinnitus

Introduction

Noise, the high exposure to which is hazardous to human health, is present in the different branches of economic activity.[1] Occupational noise exposure is one of the major contributing factors to adult-onset hearing loss and tinnitus,[2] where workers exposed occupationally to noise commonly complain of tinnitus and hearing impairment.[1] Noise-induced hearing loss (NIHL) may be accompanied by psycho-social consequences, such as social isolation, frustration, and depression.[3]

It is known that NIHL may be mediated by the interaction of genetic and environmental factors,[4,5] but the mechanisms involved are still not clearly understood. It has been suggested that the etiopathogenesis may include a direct mechanical injury to the cochlea, inner ear cell apoptosis and necrosis resulting from oxidative stress, or metabolites released during signal transduction.[5,6]

Tinnitus, a common and annoying accompaniment of hearing loss, is an auditory phantom sensation defined as 'ringing in the ear'. It is a frequent disorder that affects all strata of the population and is a major health concern. It is often linked to different forms of hearing loss of varying degrees of severity.[7] Hearing loss and acoustic environmental exposures are causing increasingly known health disorders.[8]

Noise-induced and age-related hearing loss https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5484347/- lary26256-bib-0012 can be differentiated by the presence of audiometric notches.[9] In the clinic, a notch is often regarded as a strong indication of NIHL. Philips et al.[10] postulated that the audiometric notch may be regarded as a phenotype for identifying the genetic contributions to hearing loss. However, experts disagree about the definition of a true notch[11] and various definitions of notch have been put forward.[12] Recently, studies have shown that audiometric notches also occur frequently in workers who are not exposed to loud work-related noise.[11,13,14]

A relationship between prolonged working hours and hearing impairment in both low and high frequencies, with a dose–response relationship, has been detected.[15] Common causes of hearing loss in the general population include aging, a history of ear diseases, diabetes, and cigarette smoking. However, the major cause in the working population is occupational noise exposure.

Smoking is an intrinsic risk factor for hearing loss. Moreover, it may synergistically influence hearing when associated with occupational noise exposure, particularly in males and older subjects.[16] Noise over-stimulation induces inflammatory responses and the up-regulation of pro-inflammatory cytokines in the inner ear.[3]

The structure and expression of cytokines can be affected by genetic alteration, causing pathological conditions. Various studies have examined single nucleotide polymorphisms (SNPs) as risk factors for inflammatory disorders.[17–19] Those SNPs may affect the expression, secretion, and cellular transport of the interleukin-1beta (IL-1β) protein.[20]

IL-1, the gene of which is located on the long arm of chromosome 2,[21] is a polypeptide consisting of subtypes IL-1α and IL-1β, with the latter subtype being the predominant form. IL-1β is secreted mainly by macrophages, dendritic cells, monocytes, natural killer cells, and B cells. The IL-1β gene polymorphism at +3954C/T may cause a 4-fold increase in interleukin expression, increasing catabolism and resulting in structural deficit.[3] Noise exposure caused the overexpression of IL-1β, interleukin-6, tumour necrosis factor-alpha, heat shock protein 70, heat shock factor 1, and cyclooxygenase-2 in the cochlea of rats.[22]

Polymorphisms of IL-1β, IL-1 receptor 1, or IL-1 receptor antagonist are associated with an increased risk of different solid malignant tumours. Human carriers of IL-1β polymorphisms (IL-1β-511T and IL-1β-31C) show enhanced IL-1β production and increased levels of circulating cytokines, which can result in a high risk of cancers.[23]

The biological activity of IL-1 cytokines is controlled at the level of their production and the maturation of receptor binding, and through post-receptor signalling by naturally present inhibitors. The association of severe inflammatory syndromes with genetic deficiencies in some of these regulatory molecules has considerably increased our understanding of the biology of IL-1 cytokines.[24] Noise exposure induces the production of such cytokines by the cochlear structure. Consequently, these cytokines may trigger an inflammatory response and play a role in the mechanism of noise-induced cochlear injury.

This study aimed to assess hearing impairment in workers occupationally exposed to noise. Audiometric notches and IL-1β gene polymorphisms were evaluated.

Materials and Methods

The study was conducted in a spinning and weaving factory located at Kafr Hakeem in the Giza governorate. It was carried out in the open-end spinning section. All subjects filled a specific questionnaire that was designed to obtain data on their personal information, smoking habit, and detailed history of current and previous jobs. Histories of chronic drug intake, previous ear operation, pus discharge, or hearing problems were emphasised. Apart from a local otoscopic examination to exclude local ear problems, general clinical examinations were also performed. After exclusion of workers with previous ear diseases and those who reported former intake of ototoxic drugs (e.g. aspirin, quinolones, and aminoglycosides), 98 subjects were finally chosen for audiometric testing. This was done using a manual pure-tone diagnostic audiometer (Model GSI 67, Grason-Stadler, Inc., Eden Prairie, MN, USA). The subjects were tested in a sound isolation room that adhered to the American National Standards Institute requirements for an audiometric testing environment. All participants underwent pure-tone

audiometry at frequencies of 0.5, 1, 2, 3, 4, 6, and 8 KHz for both ears. Written consent was obtained from all examined subjects. Approval from the ethics committee at the National Research Centre was obtained prior to the study.

Environmental measures

Environmental noise assessment was carried out using a portable Sound Level Meter Standard (Model CR 306) at different sites in the open-end spinning sector.

Gene assessment

DNA extraction

Peripheral blood specimens from all study participants were collected into an EDTA vacuum tube, and DNA was extracted using the QIAmp extraction kit.

Genotyping of IL-1β polymorphism

IL-1β gene polymorphisms were assessed according to the methods described by Carvalho et al.[3] The C-to-T polymorphism located at the +3954 positions in the IL-1β gene was amplified, resulting in a 182 bp fragment. The polymerase chain reaction (PCR) mixture contained 1X PCR buffer, 1.5 μM $MgCl_2$, 8 μM of each deoxyribonucleotide triphosphate, 1 μM of each sense primer and anti-sense primer, and 2 units of *Taq* DNA polymerase (Invitrogen, Carlsbad, CA, USA).

The primers used were as follows: Forward 5′-CTC AGG TGT CCT CGA AAG AAA TCA A-3′ and Reverse 5′-GCT TTT TTG CTG TGA GTC CCG-3′. PCR amplification was performed in a thermal cycle under the following conditions: Initial denaturation at 95 °C for 5 min, followed by 30 cycles at 95 °C for 1 min, 67 °C for 1 min, and 72 °C for 1 min, and a final extension step at 72 °C for 5 min.

The PCR product was digested overnight with 5 units of *Taq I* polymerase (Invitrogen, Carlsbad, CA, USA) at 65 °C. The digested fragments were separated on a 2% agarose gel that was then stained with ethidium bromide and visualised under UV illumination. The gel revealed 85 and 97 bp fragments (allele C), a single 182 bp fragment (allele T), and three fragments (85, 97, and 182 bp), indicating the presence of both C and T alleles.

Statistical analysis

Statistical analysis of the data was performed using the SPSS package, version 17.0. The Chi-square test was used to compare the distributions of genotypes as well as the frequencies of alleles for the +3954 IL-1β polymorphism. The analysis of variance test was used to compare multiple variants.

Results

The environmental noise measurements revealed an elevation of the sound level at four tested sites in the open-end spinning section. The noise level ranged between 100 and 110 dB, with a mean of 105.5 dB, which exceeded the 90 dB level recommended by the Egyptian Environmental Law No.4 (1994).

Table 1: General characteristics of the examined workers.

		Mean ± SD	
Age (years)		39.47 ± 5.94	
Duration of exposure (years)		17.20 ± 4.76	
Systolic blood pressure (mmHg)		127.68 ± 17.66	
Diastolic blood pressure (mmHg)		81.78 ± 10.79	
		No	%
Smoking	Yes	21	21.4%
	No	77	78.6%
Tinnitus	Yes	27	27.6%
	No	71	72.4%
Diabetes	Yes	5	5.1%
	No	93	94.9%

Table 1 shows the general characteristics of the studied workers. The percentage of smokers was 21.4%, whereas those with diabetes constituted only 5% of the examined individuals. Workers who complained of tinnitus represented 27.6% of the studied population.

Table 2: Hearing impairment in the workers.

Hearing impairment	Right Ear	Left Ear
	No. (%)	No. (%)
Normal (0–25 dB)	36 (36.7%)	44 (44.9%)
Mild (26–40 dB)	44 (44.9%)	37 (37.7%)
Moderate (41–60 dB)	18 (18.4%)	17 (17.3%)

Table 3: Analysis of audiometric notches in the workers' audiograms.

Audiometric notch at 4000 Hz	Right ear	Left ear
	No. (%)	No. (%)
<25 dB	36 (36.7%)	47 (48.0%)
≥25 dB	62 (63.3%)	51 (52.0%)
Total	98	98

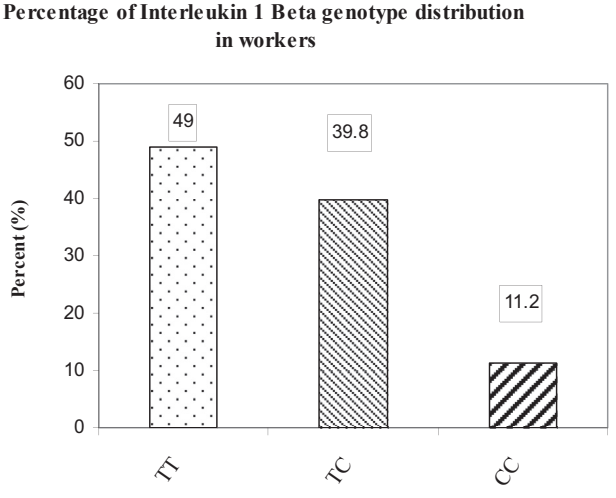

Figure 1: IL-1β genotype distribution amongst the examined workers.

Table 4: IL-1β genotype distribution according to smoking habits and audiometric notches amongst the workers.

		IL-1β genotypes			Chi square	P value
		TT	TC	CC		
		No. (%)	No. (%)	No. (%)		
Smoking	Yes	7 (14.6%)	8 (20.5%)	6 (54.5%)	8.52	0.014[a]
	No	41 (85.4%)	31 (79.5%)	5 (45.5%)		
Audiometric notch	Absent	19 (39.6%)	9 (23.1%)	0 (0.0%)	7.8	0.02[b]
	Present	29 (60.4%)	30 (76.9%)	11 (100.0%)		

[a] Highly significant.
[b] Significant.

Table 5: IL-1β genotype distribution according to workers with tinnitus complaints.

		IL-1β genotypes			Chi Square	P Value
		TT	TC	CC		
		No. (%)	No. (%)	No. (%)		
Tinnitus	Yes	9 (18.8%)	14 (35.9%)	4 (36.4%)	0.16	3.6
	No	39 (81.3%)	25 (64.1%)	7 (63.6%)		

The percentages of hearing impairment in the right and left ears of the examined workers are shown in Table 2. None of the workers suffered from profound hearing loss (i.e. of >60 dB).

Table 3 demonstrates the presence of audiometric notches in one or both ears in the examined workers. Only 28 (28.6%) of the audiograms of the workers were free of notches in both ears. Majority of the workers suffered notches of ≥25 dB in both ears (45.9%). However, 25 workers (25.5%) showed notches of <25 dB.

The TT genotype showed the highest percentage of distribution amongst the workers (49%). There was no significant difference amongst the three genotypes with regard to the mean age of the workers and duration of noise exposure (Figure 1).

Significant differences were detected amongst the three IL-1β genotypes with regard to smoking and audiometric notches, as shown in Table 4. The CC genotype was associated with smoking (54.5%) and with audiometric notches (100%).

No significant difference was observed in the IL-1β genotype distribution according to workers with and without tinnitus complaints, as shown in Table 5.

Discussion

Occupational noise is one of the most common occupational hazards worldwide.[15] Moreover, the noise is linked to numerous non-auditory health effects, such as sleeping disorders, electrocardiogram abnormalities, and hypertension.[25] Previous studies have shown that excessive noise exposure is the most pervasive preventable aetiology of hearing loss. It has been estimated that over 12% of the world population are susceptible to hearing loss from noise, where approximately one-third of all cases could be related to acoustic exposure.[26]

The prevalence and significance of hearing injuries induced by noise levels not previously known to cause permanent hearing impairment have recently become obvious. Whereas the damage to, and loss of, afferent terminals of auditory nerve fibres at the cochlear inner hair cells are well documented, the effects of noise exposure and terminal loss of the inner hair cells are less recognized.[27]

The majority of workers in the present study were non-diabetic (93%) and normotensive. Smokers represented 21.4% of the workers studied. It has been shown that cigarette smoking can hinder cochlear circulation by increasing the blood viscosity and decreasing oxygenation. Recently, cigarette smoking has been implicated in the increased susceptibility to noise damage https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5593900/- CR19. The combination of smoking and occupational noise exposure can synergistically affect hearing, especially in elderly male participants.[16] In addition, individuals with the longest acoustic exposure duration and maximum pack-years are more at risk.

A considerable portion of the workers complained of tinnitus (27.6%), denoting early symptom of hearing affection. Audiograms of the workers revealed the deterioration of hearing acuity in either the right or left ears, but none of the individuals showed a profound hearing loss. Those results are attributed to the reluctance of the workers to use the available hearing protective equipment.

A high percentage of the workers presented with audiometric notches of ≥25 dB either for the right ear (62.3%) or left ear (52.0%) or for both ears (45.9%). The appearance of such notches at a frequency of 4000 Hz has been well documented as evidence of occupational noise exposure and is considered as a classical sign of NIHL.[14,28]

In the present study, 49% of the workers had the IL-1β TT genotype and 11.2% were homozygous for the CC genotype. The heterozygous TC genotype was detected in 39.8% of the workers. Fujioka et al.[29] reported the production of pro-inflammatory cytokines, including IL-1β, in the early phase of the noise over-stimulated cochlea. These cytokines, which are generated by the cochlear structure itself in response to noise exposure, may initiate an inflammatory response and have some role in the mechanism of acoustic-induced cochlear damage. IL-1β is a mediator of both bacterial and viral otitis media. It has an influence on numerous target cells, stimulating the pro-inflammatory network in the middle ear. Hence, it could result in the activation and proliferation of fibroblasts and the growth of osteoclasts in the middle ear, possibly leading to fibrosis and bone erosion.[30]

We found that 54.5% of the workers with the CC genotype were smokers and 45.5% were non-smokers (Table 4); additionally, 36.4% complained of tinnitus whereas 63.6%

did not (Table 5). The study suggests that there is an association between polymorphisms in the IL-1β gene and smoking.

Smoking is common in all social classes, with some differences between them. Current smoking was shown to be associated with hearing impairment in both speech-relevant frequency and high frequency across all ages.[31] Recently, inflammatory responses were shown to occur in the inner ear under various injurious conditions, including noise over-stimulation. Therefore, it can be concluded that smoking represents a confounding factor, in addition to noise, in workers with the CC genotype of the IL-1β gene, causing hearing impairment.

This work is considered the first study in Egypt to have correlated audiometric notches in audiograms and gene polymorphisms in workers occupationally exposed to noise. Furthermore, a significant association was shown between workers with the C allele and audiometric notches at ≥25 dB (Table 4). These results raise the hypothesis that a particular genotype could predispose individuals to hearing impairment by enhancing the inflammatory processes.

Um et al.[32] suggested that the IL-1β-511 and + 3953 loci may play an outstanding role in the etiopathogenesis of NIHL. IL-1β is produced and released by many distinct immune and non-immune cell types as an immediate response to inflammatory signals. Bent et al.[33] demonstrated that IL-1β acted as an amplifier of immune reactions. For a fairly long time, IL-1 was widely acknowledged as being required for the effective initiation of innate immune responses and shaping of adaptive immune responses to resolve acute inflammations. However, the view of IL-1β as a beneficial immune regulator has been affronted by the finding that gain-of-function mutations in components of inflammation result in increased IL-1β production that lead to auto-inflammatory diseases.

Recommendations

Hearing conservation programs are strongly warranted in the textile industry. Hearing protective equipment should be provided to all workers. Regular follow-up is needed for workers whose audiograms present notches at their periodic hearing tests. Smoking cessation programs are important to encourage smokers to quit smoking, especially in noisy workplaces.

Conclusion

An association exists between the CC genotype and smoking as well as audiometric notches in workers occupationally exposed to noise. We suggest that an interrelationship exists amongst tinnitus, audiometric notches, and IL-1β genotypes, which requires further studies.

Source of funding

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

Ethical approval certificate (Registration Number 16401) was obtained from the Medical Research Ethics Committee.

Authors' contributions

HMA and MMT designed the study. HMA conducted the audiometry. NMA interpreted the audiogram results. MMT and KSE conducted the molecular study. All authors collected and organized the data. EME analysed and interpreted the data. MMT wrote the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Boger ME, Sampaio AL, Oliveira CA. Analysis of hearing and tinnitus in workers exposed to occupational noise. **Int Tinnitus J 2017**; 20(2): 88–92.
2. Ralli M, Balla MP, Greco A, Altissimi G, Ricci P, Turchetta R, et al. Work-related noise exposure in a cohort of patients with chronic tinnitus: analysis of demographic and audiological characteristics. **Int J Environ Res Public Health 2017**; 14(9). https://doi.org/10.3390/ijerph14091035.
3. Carvalho LC, Marchiori LL, Melo JJ, Maciel SM, Poli-Frederico RC. Interleukin-1β gene polymorphism and hearing loss related to the history of occupational noise exposure in Brazilian elderly. **Noise Health 2013**; 15(64): 160–164. https://www.ncbi.nlm.nih.gov/pubmed/?term=Carvalho%20LC%5BAuthor%5D&cauthor=true&cauthor_uid=23689297.
4. Carlsson PI, Van Laer L, Borg E, Bondeson ML, Thys M, Fransen E, et al. The influence of genetic variation in oxidative stress genes on human noise susceptibility. **Hear Res 2005**; 202(1–2): 87–96.
5. Ding E, Liu J, Shen H, Gong W, Zhang H, Song H, et al. Notch polymorphisms associated with sensitivity of noise induced hearing loss among Chinese textile factory workers. **BMC Med Genet 2018**; 19(1): 168.
6. Le Prell CG, Yamashita D, Minami SB, Yamasoba T, Miller JM. Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. **Hear Res 2007**; 226(1–2): 22–43.
7. Marchiori LLM, Dias ACM, Gonçalvez AS, Poly-Frederico RC, Doi MY. Association between polymorphism of tumor necrosis factor alpha (tnfα) in the region -308 g/a with tinnitus in the elderly with a history of occupational noise exposure. **Noise Health 2018**; 20(93): 37–41.
8. Śliwińska-Kowalska M, Zaborowski K. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and permanent hearing loss and tinnitus. **Int J Environ Res Public Health 2017**; 14(10): E1139. https://doi.org/10.3390/ijerph14101139.
9. Kirchner DB, Evenson E, Dobie RA, Rabinowitz P, Crawford J, Kopke R, et al. Occupational noise-induced hearing loss. **J Occup Environ Med 2012**; 54: 106–108.
10. Phillips SL, Richter SJ, Teglas SL, Bhatt IS, Morehouse RC, Hauser ER, et al. Feasibility of a bilateral 4000-6000 Hz notch

as a phenotype for genetic association analysis. **Int J Audiol 2015**; 54(10): 645–652. https://doi.org/10.3109/14992027.2015.1030512.
11. Osei-Lah V, Yeoh L. High frequency audiometric notch: an outpatient clinic survey. **Int J Audiol 2010**; 49: 95–98.
12. Wilson RH, McArdle R. Characteristics of the audiometric 4,000 Hz notch (744,553 veterans) and the 3,000, 4,000, and 6,000 Hz notches (539,932 veterans). **J Rehabil Res Dev 2013**; 50: 111–132.
13. Nondahl DM, Shi X, Cruickshanks KJ, Dalton DS, Tweed TS, Wiley TL, et al. Notched audiograms and noise exposure history in older adults. **Ear Hear 2009**; 30: 696–703.
14. Lie A, Engdahl B, Hoffman HJ, Li CM, Tambs K. Occupational noise exposure, hearing loss, and notched audiograms in the HUNT Nord-Trøndelag hearing loss study, 1996-1998. **Laryngoscope 2017**; 127(6): 1442–1450.
15. Park JW, Park JS, Kim S, Park M, Choi H, Lim S. The association between long working hours and hearing impairment in noise unexposed workers: data from the 5th Korea National Health and Nutrition Examination Survey (KNHANES 2010-2012). **Ann Occup Environ Med 2016**; 28: 55. eCollection 2016.
16. Wang D, Wang Z, Zhou M, Li W, He M, Zhang X, et al. The combined effect of cigarette smoking and occupational noise exposure on hearing loss: evidence from the Dongfeng-Tongji Cohort Study. **Sci Rep 2017**; 7(1): 11142.
17. Dinarelo CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. **Blood 2011**; 117: 3720–3732.
18. Chen CJ, Kono H, Golenbock D, Reed G, Akira S, Rock KL. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. **Nat Med 2007**; 13: 851–856.
19. Cohen I, Rider P, Carmi Y, Braiman A, Dotan S, White MR, et al. Differential release of chromatin-bound IL-1alpha discriminates between necrotic and apoptotic cell death by the ability to induce sterile inflammation. **Proc Natl Acad Sci USA 2010**; 107: 2574–2579.
20. Hwang JH, Chen JC, Yang SY, Wang MF, Chan YC. Expression of tumor necrosis factor-α and interleukin-1β genes in the cochlea and inferior colliculus in salicylate-induced tinnitus. **J Neuroinflammation 2011**; 8: 30. https://doi.org/10.1186/1742-2094-8-30.
21. Mahé Y, Oppenhein JJ. Interleukin 1. In: Roitt IM, Delves PJ, editors. *Encyclopedia of immunology*. 1 st ed. London: Academic Press; 1992. pp. 897–901.
22. Dogan R, Sjostrand AP, Yenıgun A, Karatas E, Kocyigit A, Ozturan O. Influence of Ginkgo Biloba extract (EGb 761) on expression of IL-1 Beta, IL-6, TNF-alfa, HSP-70, HSF-1 and COX-2 after noise exposure in the rat cochlea. **Auris Nasus Larynx 2018**; 45(4): 680–685. https://doi.org/10.1016/j.anl.2017.09.015.
23. Sun Y, Zhu D, Wang G, Wang D, Zhou H, Liu X, et al. Proinflammatory cytokine IL-1β up-regulates CXC chemokine receptor 4 via notch and ERK signaling pathways in tongue squamous cell carcinoma. **PLoS One 2015**; 10(7)e0132677.
24. Palomo J, Dietrich D, Martin P, Palmer G, Gabay C. The interleukin (IL)-1 cytokine family-Balance between agonists and antagonists in inflammatory diseases. **Cytokine 2015**; 76(1): pp25–pp37.
25. Sayler SK, Roberts BJ, Manning MA, Sun K, Neitzel RL. Patterns and trends in OSHA occupational noise exposure measurements from 1979 to 2013. **Occup Environ Med 2019**; 76(2): 118–124. https://doi.org/10.1136/oemed-2018-105041.
26. Almaayeh M, Al-Musa A, Khader YS. Prevalence of noise induced hearing loss among Jordanian industrial workers and its associated factors. **Work 2018**; 61(2): 267–271.
27. Bullen A, Anderson L, Bakay W, Forge A. Localized disorganization of the cochlear inner hair cell synaptic region after noise exposure. **Biol Open 2018**. https://doi.org/10.1242/bio.038547.
28. McBride DI, Williams S. Audiometric notch as a sign of noise induced hearing loss. **Occup Environ Med 2001**; 58(1): 46–51.
29. Fujioka M, Kanzaki S, Okano HJ, Masuda M, Ogawa K, Okano H. Proinflammatory cytokines expression in noise-induced damaged cochlea. **J Neurosci Res 2006**; 83(4): 575–583.
30. Živković M, Kolić I, Jesić S, Jotić A, Stanković A. The allele 2 of the VNTR polymorphism in the gene that Encodes a natural inhibitor of IL-1β, IL-1RA is favorably associated with chronic otitis media. **Clin Exp Otorhinolaryngol 2018**; 11(2): 118–123.
31. Chang J, Ryou N, Jun HJ, Hwang SY, Song JJ, Chae SW. Effect of cigarette smoking and passive smoking on hearing impairment: data from a population-based study. **PLoS One 2016**; 11(1)e0146608.
32. Um JY, Jang CH, Kim HL, Cho YB, Park J, Lee SJ, et al. Proinflammatory cytokine IL-1 β polymorphisms in sudden sensorineural hearing loss. **Immunopharmacol Immunotoxicol 2013**; 35(1): 52–56. https://doi.org/10.3109/08923973.2012.719523.
33. Bent R, Moll L, Grabbe S, Bros M M. Interleukin-1 beta-A friend or foe in malignancies? **Int J Mol Sci 2018**; 19(8): 24.

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