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Early Cochlear Changes In Migrain With Transient Evoked Otoacoustic Emissions

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Abstract

Objective: In this study, our objective is to examine the cochlear functions that might occur during the early period of migraine.

Methods: Our prospective study was planned as a clinical study and it was analyzed by measuring the transient otoacoustic emission of individuals who have or do not have migraine with normal audition limit as pure tone audiometry.

Results: The emission amplitudes of the patients with migraine were lower than the control group P < 0.05). Even though the difference at the frequency of 2.0 Hz on the right side was significant P < 0.05) in the statistical analysis conducted between the patients and the control group, it was not found significant at other frequencies (P >0.05). In addition, there were no statistical differences between the patients with migraine and the control groups in terms of gender and age (P >0.05).

Conclusion: Audiologic monitorisation might be required in the long-term with larger patient groups despite of the minimal changes in the cochlear function in the early stages of migraine.

Keywords: Migraine, Transient Otoacoustic Emission Testing, Hearing Loss

Migrende Transient Otoakustik Emisyon İle Erken Koklear Değişiklikler

Öz

Amaç: Bu çalışmadaki amacımız migrenin erken döneminde oluşabilecek koklear fonksiyonları incelemektir.

Yöntemler: Çalışmamız prospektif olup klinik çalışma olarak planlandı ve pure tone odyometrik olarak normal işitme sınırlarında olan migrenli ve migrenli olmayan kişilerin transient otoakustik emisyon ölçülerek analiz edildi.

Bulgular: Migrenli hastaların emisyon amplitüdleri kontrol grubuna göre düşüktü (P < 0.05). Hastalar ile kontrol grubu arasında yapılan istatiksel analizde sağ tarafta 2.0 Hz frekansında farklılık anlamlı çıkmasına (P < 0.05) karşın diğer frekanslarda anlamlı bulunamadı (P >0.05). Ayrıca cinsiyet ve yaş açısından migren hastaları ile kontrol grupları arasında istatiksel farklılık bulunamadı (P >0.05).

Sonuç: Migrenin erken dönemlerinde koklear fonksiyonlarda minimal değişiklikler saptanmasına karşın daha büyük hasta grubu ile uzun dönemde işitsel moniterizasyon ihtiyacı gerekebilir.

Anahtar Kelimeler: Migren, Transient Otoakustik Emisyon Testi, İşitme kaybı.

INTRODUCTION

Headache and dizziness are two of the most common symptoms in the general population[1]. Migraine, a chronic illness with a wide spectrum of symptoms other than headache, can occur with or without an aura. Phonophobia, a fear of loud noises, is the most common auditory symptom in migraine. However, other cochlear symptoms such as hearing loss, which are insidious and may be noticed late in the course of the condition, are discussed much less frequently. Additionally, other than phonophobia, various neuro-otological symptoms such as vertigo, dizziness, hearing loss, tinnitus, and aural pain, are also sometimes reported by patients with migraine[2,3]. Both migraine and vertigo are common in the general population, with lifetime prevalences of about 16% for migraine and 7% for vertigo[4]. The link between migraine and vertigo was recognized in the 19th century by some early neurologists[5], who discovered that symptoms related to vestibulocochlear defects can occur in the form of an aura and may or may not be accompanied by a headache[6,7].

Phonophobia is regarded as the most common auditory symptom in patients with migraine. Noise can also be an important trigger and aggravating factor in migraine patients[8,9]. Spierings et al. showed that noise is a precipitating and aggravating factor in 65% of such patients[9].

Otoacoustic emissions (OAEs) were first described by Kemp[10] and are an important non-invasive diagnostic tool that measures the functioning of the outer hair cells in the cochlea. Whereas other audiological methods cannot detect these cells, they can detected by OAEs within a few minutes in people who have audiologically normal hearing thresholds. OAEs form as a result of reversible energy transfer from the cochlea to the middle ear and occur either spontaneously within the normal hearing process or after stimulation of the ear by sound, such as narrowband tonal signals. This energy can be measured quickly using appropriate probes that are simply placed in the outer ear canal. The signals are produced by the active micromechanism of the outer hair cells of the organ of Corti[10].

Transiently evoked OAEs (TEOAEs) are used to analyze any intermediate emissions in the frequency range 1–4 kHz that occur in any way within a wide spectrum of click stimuli.

Few studies have sought to determine the relationship between chronic migraine and otological symptoms. Thus, temporary or permanent auditory manifestations associated with migraine remain largely unknown.

Our aim in this study was to monitor the cochlear function of patients diagnosed with migraine in a neurology clinic and to investigate whether these individuals experienced auditory complications at an early stage of their condition. All patients were followed by the clinic and had normal hearing values according to pure tone audiometry performed with transient OAEs at the early stage.

METHODS

This study was prospective clinic study that approved by the XXX University Faculty of Medicine Ethics Committee (approval number 149 dated 25.03.2013). The participants included 27 female and 6 male patients who were admitted to the XXX University Faculty of Medicine Hospital Neurology Clinic between June 2013 and December 2017 and were followed by the same doctor for a migraine diagnosis. In addition, there were 31 control subjects (23 females and 8 males, comprising 62 ears),

who were members of the same university, underwent TOAE testing, and had normal otoscopic examinations and normal pure tone audiometry.

The migraine diagnosis was made according to the International Classification of Headache Disorders-3 (beta version) codes 1.1, 1.2, and 1.3 and the A1.6.6 criteria; patients who had a visual aura but did not have other neurological symptoms were included in the study [11] . Patients with codes 1.4 and 1.5 of probable migraine were excluded. All participants provided signed informed consent forms.

The inclusion criteria were: diagnosis of migraine according to the neurology guidelines mentioned above, not taking any prophylactic medications, and no history of an attack within the previous 3 days.

The exclusion criteria were: neurological symptoms in addition to migraine, ear pathologies affecting hearing, ear surgery, head trauma, noise exposure, use of ototoxic or vestibulotoxic medications, diabetes affecting the inner ear, or systemic diseases, including autoimmune conditions. Patients in the acute stage of phonophobia and headache, as evidenced by associated phonophobia or other complaints during the emission test, were also excluded from the study. Thus, the otoacoustic emission test was performed on stable patients with complaints such as hearing loss, dizziness, and headache.

Statistical Analyses

Statistical evaluation was carried out using Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows Inc. (Chicago, IL, USA). Results were analyzed statistically by Mann-Whitney U test which overall group comparisons between migrain patients and controls for data that were not normally distributed. Thus results to determine differences in amplitudes and SNR (signal-to-noise ratio)'s of TOAE and corresponding noise floor differences and thresholds for each frequency. Categor¬ical variables was analysed by using chi-square test. We analyzed between two groups according to sex by independent two sided by student t test. Also we used pearson correlation test between duration of migraine and ear emission results. Because data that were distributed normally. A P-value less or equal to 0.05 was considered statistically significant.

RESULTS

The mean age of the migraine patients was 36.8 (range, 23–48) years, and that of the control group was 33.2 (range, 25–51) years; the sex distributions of the two groups were matched. In total, 33 migraine patients (27 women and 6 men) were included in the study, and 66 ears were tested. The demographic characteristics of the patients are shown in Table 1. The average time elapsed before migraine diagnosis was about 44 months. The emission amplitudes (SNR-Signal-to-noise ratio) of the patients with migraine were low compared to those of the control group. Although the TOAE scan revealed a significant difference between the patient and control groups in the 2.0-Hz frequency of the right ear, no difference was found at other frequencies ($P < 0.05$; Table 2). No significant differences in sex ratio or age were observed between the patient and control groups ($p>0.05$), except for the right ear 2.8.1 ($P = 0.015$; Table 3). No correlation was detected between duration of migraine and ear emission results (Table 5; $P > 0.05$).

DISCUSSION

The relationship between migraine and vestibular symptoms was first described in 1984 by Kayan and Hood. According to them, symptoms related to vestibulocochlear defects can occur in the form of an aura that accompanies a headache or can occur without a headache[5,6].

Auditory symptoms are among the most common symptoms of migraine and can be part of migraine diagnosis. People with phonophobia are disturbed by others' voices,[8] but the mechanism background of phonophobia in patients with migrane is not well understood. Along with headache, a change in the blood flow to the cochlear vessels, due to the activation of trigeminal sensory innervation or vascular permeability, and a vasospasm of the internal auditory arterial branches or any migrainous infarction have been considered among the possible mechanisms of vestibulocochlear deficit in patients with migraine.

OAEs are sensitive for evaluating cochlear functions[12] and are important for objectively and dynamically monitoring patients before important and functional hearing losses develop for any reason[12,13].

Several studies have examined the auditory systems of patients with migraine using auditory brainstem responses (ABRs) and OAEs, and the results suggest that subclinical dysfunctions of the cochlear and auditory pathways are related to migraine[11,12]. So we were considered, TEOAEs on all patients with migraine and control groups who had normal pure tone audiometry thresholds. It is important to take precautions before complications occur in conditions such as migraine.

Bolay et al.[14] who conducted both DPOAEs and TOAEs, detected changes in distortion product otoacoustic emissions (DPOAEs) on scans only at 5 kHz. They reported that DPOAE amplitudes decreased, but no threshold differences were detected in the emissions. Jofilly et al.[15] performed a prospective case-control study of 29 women with migraine and phonophobia and 26 healthy women; participants were subjected to TEOAE testing at frequencies from 1 to 4 kHz. The authors calculated average TEOAE amplitudes under conditions with and without exposure to contralateral noise. However, no differences were detected between the groups. The magnitude of TEOAE suppression was lower in the migraine group, but only at 1 and 1.5 kHz ($p = 0.042$ and $p = 0.004$, respectively). We found a significant difference in the emission of frequencies at 2.0 kHz in the right ear, as the waves were small compared to those in the control group ($P < 0.05$). This result is consistent with the results of the study by Bolay[14]. Also our study is consistent with Joffilly et al[15] who found a difference only at 5 kHz in their study, which was performed using DPOAE and 1 and 1.5 kHz with TEOAE. Therefore, the relevant results are in accordance with the results of our study. Our study model is different that we analyzed emission results in patients who were audiologically within normal limits. These results show that, over the long term, changes may occur at additional frequencies in patients with migraine and that there may be changes in certain areas of the cochlea. Indeed, OAEs can detect early changes in the cochlea. The duration of illness may also contribute to the occurrence of complications; 44 months is considered an early stage in a chronic and slowly progressing illness such as migraine, and our aim was to detect changes that occur during the early stage. Age is another important factor that affects the course of some diseases. However, by coincidence, our sample of patients was 30–50 years of age. Thus, this factor did not affect our statistical results. Also gender is other factor which can be a risk factor in some diseases such as migraine. So we found significant statistical difference in just at the right ear 2.8.1 ($P = 0.015$; Table 3). Also this result was early result. The emission of 2.8.1 frequency is represent high frequency of cochlea area. However; this significance is early result for gender like other factors. Hamed et al.[16] detected for low emissions at more than one frequency, such as at 1.3 and 4 kHz. Hamed's study results are consistent with ours, but they obtained results at more than one frequency. This partial difference can be attributed to patient demographics, such as the duration of experiencing migraines. There were differences in emission amplitudes between the patient and control groups and the changes for 2-Hz frequencies in the right ear were significant. However, the average follow-up period of patients in the study performed by Hamed et al.[16] was 8.3 years, which was longer than the average duration of illness in our study; our study also involved

participants's age differed from those in Hamed et al.'s study. As a result, differences were detected at 4 kHz in the TOAE, whereas they detected differences in the DPOAE between the patients with migraine and the control group at 1, 1.5, 2, 3, and 5 kHz. Additionally, they found latencies in the I–III waves of the ABRs and a time difference between waves I and V. Therefore, changes due to cochlear involvement can occur in migraine depending on time and may be associated with chronic migraine.

OAE allows for early detection of differences that cannot be found using pure tone audiometry or speech discrimination. OAE constitutes the peak activity of the outer hair cells. Drops in OAE waves can be detected before changes in pure tone audiogram thresholds appear, and this is significant when educating and monitoring patients[13].

Migraines can be caused by changes in the brainstem and interactions with major sensorial pathways such as those related to acoustics or light[17]. The mechanism of cochlear involvement in migraine is still not fully understood. Some theories point to a vascular mechanism, assuming migraine to be a malfunction of cerebral vascular reactivity[18]. For example, ischemia is the cause of temporary hearing loss in basilar migraine, and ischemia is associated with cAMP and activation of central nervous system adrenoceptors, including changes in calcium metabolism[2]. Hamed et al.[16] suggested that subclinical changes in cochlear function and auditory pathways are associated with chronic migraine. It is possible that migraine is accompanied by a compromised blood supply to the auditory system[16]. One study demonstrated support for the notion of interictal auditory sensory dysmodulation as a yet unidentified subset of migraine, including vestibular migraine[19].

Sterile edema and exudate accumulation as a result of massive local adrenaline release and stimulation of beta receptors are pathognomonic signs of migraine that are visible using an ophthalmoscope[20]. This mechanism has been elucidated by the following findings. In a rat study, TOAE and ABR indicated that adrenaline and intra-arterial perfusion changed blood flow and hearing sensitivity. In rats, propranolol HCl and potent beta blockers have been found to be protective and effective against hearing fluctuations in migraine attacks[20].

Post-mortem examinations of patients with endolymphatic hydrops, sudden hearing loss, and migraine revealed fibrosis associated with old infarcts in the cochlea[21]. The authors concluded that sudden hearing loss in patients with migraine is related to the ischemia caused by the vasospasm associated with migraine[22]. The cochlea is an organ that receives its blood supply through a specific vascular structure, such as terminal capillaries. Under ischemic conditions, such as a change in minimal blood flow, the high metabolic needs and genetic characteristics of the inner ear cannot compensate for microvascular complications before they become pronounced[23,24].

Cochlear injury and auditory dysfunction in migraine are related to an inflammatory reaction in the brain or the release of vasoactive mediators (histamine, serotonin, and plasma quinines) due to cerebral vasospasm and a reduction in blood flow, temporary vasodilatation of small vessels, or a defect in vascularity[25]. Scher et al.[26] reported that migraine exacerbates atherosclerosis. Hearing impairment can increase with increased exposure to noise in daily life[27].

As shown by our patient profile and emission results, factors such as the age of patients and illness duration may contribute to hearing loss in migraine. Therefore, changes involving different frequencies may be detectable by emission scans at the 10-year follow up and beyond.

Although our study provides important results, it also has several limitations. A relatively small group of patients was included, and patient consent could not be obtained for the ABR testing to discern retrocochlear pathology. Indeed, as mentioned above, Hamed et al.[16] detected cochlear changes as well as changes in the auditory pathways in patients with migraine. Additionally, Dash et al.[28]

detected changes on ABR, such as prolonged latency waves, in patients with vertigo and migraine. However, the most important and distinctive finding of our study, which distinguishes it from other studies, is the arly OAE changes.

CONCLUSION

As a result, we were able to determine outer hair cell function within a few minutes; therefore, OEAs can be used to detect hearing changes in patients with migraine in clinical settings during the early stage so they can be monitored. Although our findings are important in terms of allowing necessary precautions to be taken and raising awareness concerning hearing changes during migraine, they need to be supported by data from a larger group of patients, additional electrophysiological tests, and long-term follow up.

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Table 1: The demographic characteristics of the patients

Demographic and Clinical characteristics of Migrain	(n=33)
Male/female	6/27

Family history of migraine	5 (15.15%)
Age, years	23–48 (36.80 ± 9.17)
Duration of illness, years	2–7 (5.33 ± 4.47)
Type of migraine	
Common migraine Typical migraine	26 (78.78%) 7 (21.21%)
Auditory symptoms Tinnitus Phonophobia	 3 (9.09%) 5 (15.15%)
Basic audiological evaluations	PTA
Right ear Left ear	 12 dB 11 dB
Tympanometry:	Tip A
Acoustic reflex:	N
Speech audiometry (range, mean ± SD) Right ear Left ear	92.00–100.00 (98.52 ± 1.84) 91.00–100.00 (98.54 ± 1.22)

Table 2: Mean otoacoustic emissions of statistical analyses of patient and control groups

Frequency	**Patient** **Mean SNR ±S.D.**	**Control** **Mean SNR ±S.D**	**P**
Right Emis.1.0.1	6.95±8.05	9.38±5.9	0.279
Right Emis.1.4.1	13.08±5.558	12.36±3.9	0.313
Right Emis.2.0.1	**14.55±6.21**	**12.95±3.89**	**0.014**
Right Emis.2.8.1	11.02±5.14	10.85±3.42	0.285
Right Emis.4.0.1	7.59±6.29	7.75±5.75	0.788
Left Emis.1.0.1	6.56±9.08	9.95±9.45	0.183
Left Emis.1.4.1	12.70±7.98	11.42±6.25	0.920
Left Emis.2.0.1	12.53±6.55	13.28±5.49	0.568
Left Emis.2.8.1	9.49±7.49	12.10±5.03	0.170
Left Emis.4.0.1	6.1±6.57	7.48±5.03	0.742

shows mean SNR (signal-to-noise ratio) results and statistical analyses of patient and control groups

Table 3: The results of statistic that between control and patient in term of gender

Frequency	**Sex**	**N**	**Mean**	**P**
Right Emis.1.0.1	0	50	7.8320	0.334

	1	14	8.7429	
Right Emis.1.4.1	0 1	50 14	12.8160 11.2786	0.380
Right Emis. 2.0.1	0 1	50 14	13.7340 11.5429	0.685
Right Emis. 2.8.1	0 1	50 14	11.4040 8.3286	0.015
Right Emis.4.0.1	0 1	50 14	8.4380 5.9714	0.229
Left Emis. 1.0.1	0 1	50 14	8.7140 7.9500	0.942
Left Emis. 1.4.1	0 1	50 14	13.3000 10.2357	0.306
Left Emis. 2.0.1	0 1	50 14	12.9420 13.6571	0.935
Left Emis. 2.8.1	0 1	50 14	10.5600 11.5929	0.981
Left Emis. 4.0.1	0 1	50 14	6.8560 6.8286	0.795

shows the results of statistic that between control and patient in term of sex. The difference was significant at the right 2.8.1 frequency.

1: male; 0: female

Table 4: The statistical correlation results between duration of migrain and ear emissions

Frequency	**Duration**		
	r	**N**	**P**
Right Emis.1.0.1	**0.225**	**33**	**0.2017**
Right Emis.1.4.1	**0.232**	**33**	**0.194**
Right Emis. 2.0.1	**0.195**	**33**	**0.276**
Right Emis. 2.8.1	**0.180**	**33**	**0.315**
Right Emis.4.0.1	**0.274**	**33**	**0.123**
Left Emis. 1.0.1	**0.199**	**33**	**0.267**

Left Emis. 1.4.1	**0.215**	**33**	**0.229**
Left Emis. 2.0.1	**0.114**	**33**	**0.529**
Left Emis. 2.8.1	**0.139**	**33**	**0.441**
Left Emis. 4.0.1	**0.328**	**33**	**0.062**

shows the statistical correlation results between duration of migrain and ear emissions.

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).