Can BRCA Mutation be a Risk Factor for Otosclerosis?

BRCA Mutasyonu Otoskleroz İçin Risk Faktörü Olabilir mi?

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ABSTRACT

Objective: The aim of this study was to investigate the presence of otosclerosis in patients with BRCA mutation.

Material and Methods: Auditory functions were compared between patients with BRCA mutation who were operated due to breast cancer and healthy controls. The study included a total of 40 individuals, among those, 20 were healthy controls, and 20 had BRCA 1 and BRCA 2 mutation. All participants were female in both groups. Age range was 25-38 years, and mean age was 31.7±3.5 years. Mean age among patients with BRCA mutation and healthy controls were 34±2.7 and 29.4±2.5, respectively. All participants were undertaken head-neck examination, pure-tone audiometry, acoustic reflex and tympanometry tests. Patients with acute and chronic otitis media, head and neck trauma, drug use that may lead to hearing impairment, and ear operation history were excluded from the study.

Results: All participants of both groups revealed type A tympanometry, normal acoustic reflex, and a normal auditory level (≤ 20dB). No statistically significant difference was observed in the bone and airway levels between 250 Hz - 2000 Hz between healthy controls and patients with BRCA mutation.

Conclusion: No significant difference was observed in the pure-tone audiometry between patients with BRCA mutation and healthy controls. Further and histopathologic studies may be needed to demonstrate the presence of otosclerotic focus in patients with BRCA mutation.

Key Words: BRCA, Otosclerosis, Osteoprotegerin

ÖZ

Amaç: Bu çalışmanın amacı BRCA mutasyonu olan hastalarda otoskleroz varlığını araştırmaktır.

Gereç ve Yöntemler: BRCA mutasyonu olan ve meme kanseri nedeniyle opere edilen hastalar ile sağlıklı kontrol grubu arasında işitsel fonksiyonlar karşılaştırıldı. Çalışmaya 20 sağlıklı kontrol ve 20 BRCA 1 veya BRCA 2 mutasyonuna sahip toplamda 40 birey dahil edildi. Her iki grup, yaş aralığı 25-38 arasında ve yaş ortalaması 31.7±3.5 yıl olan kadın katılımcılardan oluşturuldu. BRCA mutasyonuna sahip hastaların yaş ortalaması 34±2.7 iken sağlıklı kontrollerin yaş ortalaması 29.4±2.5'di. Tüm katılımcılara baş-boyun muayenesi, saf ses odyometrisi, akustik refleks ve timpanometritestleri yapıldı. Akut ve kronik orta kulak iltihabı, baş ve boyun travması, işitme bozukluğuna yol açabilecek ilaç kullanımı ve kulak operasyon öyküsü olan hastalar çalışma dışı bırakıldı.

Bulgular: Her iki gruptan da tip A timpanometri, normal akustik refleks ve normal işitme seviyeleri (≤ 20dB) elde edildi. Sağlıklı kontroller ile BRCA mutasyonu olan hastalar arasında 250 Hz - 2000 Hz arasındaki kemik ve hava yolu düzeylerinde istatistiksel olarak anlamlı bir fark gözlenmedi.

Sonuç: BRCA mutasyonuna sahip hastalar ile sağlıklı kontroller arasında saf ses odyometri sonuçları açısından istatiksel anlamlı farklılık saptanmadı. BRCA mutasyonu olan hastalarda otosklerotik odak varlığını göstermek için ileri ve histopatolojik çalışmalar gerekebilir.

Anahtar Sözcükler: BRCA, Otoskleroz, Osteoprotegerin

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INTRODUCTION

Otosclerosis is the bone remodeling disease observed in the otic capsule of humans (1). Two phases may be defined for the otosclerotic lesions in and around the stapes histologically and these include the early spongiotic phase (otospongiosis) and a late or sclerotic phase (1, 2). Spongiotic bone includes many fibrocytes and osteoclasts placed within large cavities or acellular cavitating areas, but most of the cells show osteoblastic lineage (3). Remodeling occurs within these foci continuously, which in turn results in dense mineralized bones (sclerosis) (4).

Osteoprotegerin (OPG) plays a key regulator role in bone metabolism with receptor activator of nuclear factor Kappa B (RANK) and RANK ligand (RANKL) (5). OPG is a soluble, neutralizing antagonist that competes with RANK localized on preosteoclasts and osteoclasts for RANKL, which is produced by osteoblasts. OPG is responsible for inhibiting the differentiation, survival, and fusion of osteoclastic precursor cells and suppressing the activation of and inducing apoptosis of osteoclasts (6).

The physiological balance between bone destruction by osteoclasts and bone formation by osteoblasts is maintained by the interaction of RANKL, RANK, and OPG (6). Osteoprotegerin knockout mice studies have demonstrated abnormal remodeling of the bone within the otic capsule with multiple foci (7). The remodeling process which was observed to be active in the OPG knockout mice mimics the otosclerosis observed in human temporal bones (7). Women with mutant breast cancer susceptibility genes, BRCA1 or BRCA2, have a high lifetime risk of breast cancer, compared to women in the general population (8).

In a study investigating the role of the OPG gene in otosclerosis, the gene was observed to be significantly decreased in cases with otosclerosis (9). Low serum levels of OPG have been demonstrated in patients with the BRCA mutation previously (10). Starting at that point, in our study we aimed to investigate whether patients with BRCA mutation had otosclerotic findings or not.

MATERIALS and METHOD

A total of 20 subjects with the BRCA 1 or BRCA 2 mutation among women operated due to breast cancer in the general surgery department and 20 healthy controls were included in the study. All participants underwent head and neck examination, pure-tone audiometry, and acoustic reflex and tympanometry tests. Pure-tone audiometry (PTA) was performed to all patients for both ears starting with 250 Hz until 8000 Hz frequency. Air and bone conduction values of pure-tone audiometry between 250 and 2000 Hz were compared between the patient group and control group.

BRCA test

The American College of Medical Genetics and Genomics (ACMG) 2017 Guidelines was used for the evaluation of the variants. Illumina Miseq technology was used for the Next Generation Sequencing procedure, and values for each patient were read at a minimum of 100X depth. Regions coding the related genes and exon-intron borders were evaluated. Gene regions were analyzed using the Next Generation Sequencing (NGS) technology. Peripheral blood samples were collected, and DNA isolation was performed according to the standard protocols of the PureLink® Genomic DNA (Thermo Fisher Scientific) kit. Sequencing was performed using the Next Generation Sequencing Illumina TruSight Cancer panel and V2 chemicals.

Statistical Analysis

The IBM SPSS Statistics Version 22 (IBM Turkish Limited Company, Istanbul, Turkey) program was used for statistical analysis. The normal distribution suitability of the parameters was evaluated by the Shapiro-Wilks test. Descriptive statistical methods (mean, standard deviations, and median value) were calculated. The Mann-Whitney U test was used in the comparison of nonparametric data between groups. Significance was assessed at the $p < 0.05$ level.

RESULTS

All patients were female in both groups. The age range was 25-38 years, and the mean age was 31.7±3.5 years. The mean age among patients with BRCA mutation and healthy controls was 34±2.7 and 29.4±2.5, respectively.

There was no significant difference between the groups in right and left air-bone conduction between 250 and 2000 Hz. (Table I).

DISCUSSION

Otosclerosis is a disease characterized by impaired bone remodeling of the human otic capsule, which leads to loss of progressive transmission and sensorineural auditory function as a result of endosteal involvement accompanied by cochlear bone resorption and fixation of the stapes base. Otosclerosis is 2-3 times more common among women than men. This may be due to hormonal reasons. Otosclerosis is an organotrophic situation and is specific to the ear only; it is not observed in other skeletal structures (11).

Clinical otosclerosis is observed in less than 0.5% of the general population. However, development of a silent otosclerotic focus may be more common (12). The incidence of histological otosclerosis has been reported to be between 8 and 11% in unselected large autopsy series (12). Otosclerosis has been reported in the stapes base (95%), round window (40%), ending of the oval window

(90%), pericochlear area (15%), and perilabyrinth area (35%) (12). Histopathologically, high cellularity and osteolytic bone lesions are present in these focal areas (12). It has been accepted that correct discriminative diagnosis of otosclerotic and non-otosclerotic stapes fixation cannot be made with magnetic resonance imaging (MRI) or audiometry tests, but can be made with surgical excision of the ankylotic stapes and subsequent histopathological examination (13). Duration of hearing loss and audiological abnormalities were demonstrated to be significantly correlated with the degree of stapes fixation (13). Clinical findings and other diagnostic tests cannot make a precise discrimination of otosclerotic or nonotosclerotic stapes fixation. Histopathological and molecular biological tests are therefore the basic methods in determining the etiology of otosclerosis (14).

Osteoprotegerin is a glycoprotein which is also known as TNFRSF11b. Osteoprotegerin inhibits formation of osteoclasts and osteolysis and induces apoptosis of osteoclasts (15). Studies have demonstrated that the bone remodeling process is tightly controlled by the critical osteoprotegerin (OPG), nuclear factor kappa B receptor activator (RANK), and nuclear factor kappa B ligand system receptor activator (RANKL) (15-16). OPG is a soluble factor and a competitive inhibitor for the RANKL receptors on osteoblasts against RANK and is a strong inhibitor of bone remodeling (16). Excessive expression of OPG leads to osteopetrosis, whereas decreased expression leads to osteoporosis (16). OPG content of the otic capsule, which is 20 times higher than other bones, may explain the little remodeling observed in the otic capsule (17).

Abnormal remodeling of bone within the otic capsule with multiple foci has been observed in studies conducted on osteoprotegerin knockout mice, and have shown osteoclastic bone resorption and formation of new bone. Additionally, OPG knockout mice have a progressive and severe hearing loss compared to controls, as determined by ABR and DPOAE tests (7). Studies have also demonstrated that OPG levels were low in patients with otosclerosis at both the tissue and gene level (18, 19). In a histopathological study conducted on 41 patients, OPG levels observed in tissue cultures were lower in patients with active otosclerosis compared to those with inactive otosclerosis (20).

Women with BRCA1 or BRCA2 mutation are at higher risk of breast cancer compared to the normal population (21). In the study of Widschwender et al., serum OPG

Table I: Evaluation of study parameters between groups.

	Control group	BRCA group	p
	Mean±SD	Mean±SD	
Right 250 Hz Air	10.55±5.56	14.5±4.83	0.17
Right 250 Hz Bone	10.2±6.2	14.75±4.72	0.20
Right 500 Hz Air	9.4±4.9	12.5±4.72	0.40
Right 500 Hz Bone	9.35±4.93	11.25±5.34	0.21
Right 1000 Hz Air	7.9±5.45	8.5±6.5	1.000
Right 1000 Hz Bone	8.3±5.6	9.25±6.9	0.84
Right 2000 Hz Air	9.5±3.96	10.5±3.2	0.31
Right 2000 Hz Bone	8.3±4.64	7.75±4.43	0.69
Left 250 Hz Air	10.05±5.67	10.7±7.91	0.67
Left 250 Hz Bone	8.6±6.61	11±7.24	0.35
Left 500 Hz Air	7.65±6.1	10.1±6.4	0.27
Left 500 Hz Bone	7.45±6.04	9.55±6.3	0.34
Left 1000 Hz Air	7.4±6.6	5.5±5.1	0.46
Left 1000 Hz Bone	8.4±6.7	11.15±6.9	0.22
Left 2000 Hz Air	8.15±5.47	7.6±5.32	0.92
Left 2000 Hz Bone	6.55±4.7	7.05±5.31	0.79

Mann Whitney U Test, *****p<0.05, **SD:** Standard Deviation

levels were demonstrated to be lower in patients with the BRCA mutation (10). In another study, lower serum OPG levels, as well as higher risk of breast cancer were demonstrated in patients with BRCA mutation (22). Our study is the first to investigate the relationship between BRCA mutation and otosclerosis. We investigated whether the OPG dysregulation observed in patients with the BRCA mutation could lead to a situation similar to otosclerosis or not. There was no significant difference between the BRCA mutated patients and the healthy control group regarding pure-tone audiometry findings. The reason we failed to demonstrate the presence of otosclerosis in patients with BRCA mutation via audiological tests may be the very low rate of clinical otosclerosis among these patients with otosclerosis and inability to demonstrate the local tissue effects of OPG dysregulation on the cochlea caused by the BRCA mutation. Thus, further studies with larger sample size, including serum osteoprotegerin levels and histopathological evaluations, should be conducted on patients with the BRCA mutation.

CONCLUSIONS

No significant difference was observed in pure-tone audiometry between patients with the BRCA mutation and healthy controls. Further and histopathologic studies may be needed to demonstrate the presence of an otosclerotic focus in patients with the BRCA mutation.

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