INTRODUCTION

Benign paroxysmal positional vertigo (BPPV), originating from the peripheral vestibular system, is a common type of vertigo. At present, the widely accepted theory about the pathophysiology of the disease is the separation of the otoconia and otoconial debris from the neuroepithelial membrane of the utricular or saccular macula [1]. The otoconia, freely floating in the semicircular canal or sticking to the cupula, provoke short-term nystagmus and vertigo [2]. Due to the topography of the semicircular canals, freely floating otoconia more frequently move into the posterior semicircular canal than into the lateral semicircular canal [3]. The affected canal determines the clinical presentation and direction of nystagmus.

The mechanism resulting in the separation of the otoconia from the neuroepithelial membrane is not yet clear. According to some studies, the separation takes place due to changes in the structure of the otoconia (e.g., osteoporosis, osteopenia, calcium metabolism disorders, or vitamin D deficiency) [4]. Additionally, head trauma and whiplash injuries can cause otocional fragmentation without neuroepithelial degeneration [5, 6].

However, several studies have proposed that degenerative changes of the neuroepithelial membrane are the main reason behind the separation of the otoconia [7-10]. Aging, diabetes mellitus, hypertension, thyroiditis, hyperlipidemia, stroke, osteopenia, osteoporosis, and vitamin D deficiency are responsible for causing the degenerative changes of the neuroepithelial membrane [11-15]. In particular, over the last 15 years, several studies have investigated the role of vitamin D deficiency and osteoporosis [4, 15-18].

Apart from the most widely accepted theory, there have been other theories about the pathophysiology of BPPV. A temporal bone study conducted by Gacek [19] in 2013 showed focal degenerative changes in the vestibular nerve axons of BPPV patients. Gacek [19] pointed out that some BPPV patients did not benefit from repositioning maneuvers, and in his temporal bone study, no debris...
The vestibular-evoked myogenic potential (VEMP) test is an emerging test that allows the specific evaluation of vestibular end organs [20]. VEMPs are recorded by electromyography (EMG) and are derived from the reflex tonic contractions of the sternocleidomastoid (SCM) and ocular muscles evoked by loud auditory stimuli. There are two kinds of VEMPs, ocular VEMP (oVEMP) and cervical VEMP (cVEMP), related to the contracted muscle groups seen by EMG [20, 21]. Murofushi et al. [22] showed that cVEMP is a test of the sacculocollic reflex to sound stimulation, which includes a reflex arc of the saccule, inferior vestibular nerve, and SCM muscle. In contrast, oVEMP recorded from the extraocular muscles is a test of the utriculo-ocular reflex to sound stimuli and has a reflex arc of the utricule, superior vestibular nerve, and extraocular muscles [23, 24].

There has been a wide consensus about the mechanism of nystagmus and clinical presentation of BPPV, but the neuroepithelial pathophysiology of BPPV still remains unclear. In this study, we aimed to clarify the pathophysiology of BPPV by evaluating the cVEMP findings of patients.

MATERIALS AND METHODS

Subjects

This study was conducted between July 2014 and October 2014 at Haseki Training and Research Hospital. Thirty-six idiopathic BPPV patients were included (26 females and 10 males), with an average age of 47.2 years (range, 20–63 years). The control group comprised 13 female and 7 male healthy volunteers with an average age of 45.1 years (range, 22–63 years). The patient and control groups were age- and sex-matched, with no statistically significant age or sex differences (p=0.490 and 0.860, respectively) (Table 1).

All participants had undergone a neurotological examination, pure tone audiometry, a bithermal caloric test, and a bilateral cVEMP recording.

Exclusion criteria included neurologic and/or otologic disorders, hearing loss documented by pure tone audiometry, history of head and/or neck trauma, chronic systemic diseases, and drug usage affecting the vestibular system. Due to the higher incidence of VEMP abnormalities in elderly people, subjects over the age of 65 years were excluded. Subjects with 20% or higher canal paresis detected by the bithermal caloric test were also excluded.

Benign Paroxysmal Positional Vertigo was diagnosed by the patient history, the Dix–Hallpike test and the head-roll tests. Thirty-four of the 36 patients had posterior canal BPPV, and two had lateral canal BPPV. cVEMPs were recorded before canalmith repositioning maneuvers were performed.

Three groups were created for the evaluation of the VEMP test. Groups one and two comprised 36 BPPV patients in total with both affected and unaffected ears, while group three comprised volunteers with bilateral healthy ears (a total of 40 healthy ears).

Our study was reviewed and approved by the Local Ethics Committee (reference number: June-2014/57). In accordance with the December 2014 guidelines, our study was reviewed and approved by the Local Ethics Committee with bilateral healthy ears (a total of 40 healthy ears). The latencies of the first positive (p1) and negative (n1) peaks and the normalized peak-to-peak (p1-n1) amplitudes were measured for the 500 Hz frequency. Because background muscle activities could interfere with the VEMP amplitudes, the interpeak amplitudes were normalized to 100% using the formula described by Murofushi et al. [22].

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\text{Asymmetry Ratio (AR\%) = } 100(Au - Aa)/(Au + Aa)
\]

Au: p1-n1 (the peak-to-peak amplitude of the unaffected ear)
Aa: p1-n1 (the peak-to-peak amplitude of the affected ear)
Statistical Analysis

Statistical analyses were performed using statistical software (SPSS 22.0, SPSS Inc.; Chicago, IL, USA). A significant difference was defined as \( p<0.05 \). The mean, standard deviation, median, minimum value, maximum value, frequency, and ratio were used for the definitive statistics of the data. The Kolmogorov–Smirnov test was used for the distribution of the variables, while the Kruskal–Wallis test, Mann–Whitney U test, and free samples t-test were used for the analysis of quantitative data. The Chi-square test was used for the analysis of qualitative data.

RESULTS

p1 and n1 Latencies

The p1 latencies for the BPPV-affected ears, unaffected ears, and controls were 14.2±1.7 ms, 14.7±1.8 ms, and 14.0±1.3 ms, respectively. The p1 latencies did not differ among these three groups (\( p=0.271 \)) (Table 2, Figure 1).

The n1 latencies for the BPPV-affected ears, unaffected ears, and controls were 21.9±2.0 ms, 22.4±2.2 ms, and 21.8±1.7 ms, respectively. The n1 latencies did not differ among these three groups (\( p=0.641 \)) (Table 2, Figure 2).

Amplitudes

The averages of the normalized amplitudes of cVEMP in response to 500 Hz air conducted stimuli (ACS) in the affected ears, unaffected ears, and controls were 0.6±0.3 µV, 0.7±0.3 µV, and 1.0±0.4 µV, respectively. In response to 500 ACS, the amplitudes in the affected ears were not different from those in the unaffected ears (\( p=0.467 \)), but the amplitude responses in the affected and unaffected BPPV ears were significantly lower than those in the controls (\( p<0.001 \)) (Table 2, Figure 3).

Amplitude Asymmetry

The amplitude asymmetry rates between the right and left ears were calculated for all participants in the BPPV and control groups. The average amplitude rates for the BPPV and control groups were 16.6±12.8 and 16.7±13.4, respectively. The average amplitude asymmetry rates were not different between these two groups (\( p=0.738 \)) (Table 3).
Changes in the affected ears of BPPV patients. Yetiser et al. [2], Kim et al. [7], Lee et al. [8] and Akkuzu et al. [10] detected lower interpeak amplitudes in BPPV have been reported in these studies at 10–50% [2, 8, 10]. Similarly, we could not detect any prolongation in the p1 and n1 latencies; however, in recent studies, no alternation in latencies was reported [2, 10, 26-29].

There have been several studies discussing cVEMP findings in BPPV patients. Abnormal VEMP findings such as prolonged p1 and/or n1 latencies, decreased interpeak amplitudes, and asymmetric responses in BPPV have been reported in these studies at 10–50% [2, 8, 10]. However, these studies are thoroughly analyzed, some data regarding the affected and unaffected ears of BPPV patients are controversial.

The first studies on cVEMP abnormalities in BPPV showed prolonged p1 and n1 latencies; however, in recent studies, no alternation in latencies has been reported [2, 10, 26-29]. Similarly, we could not detect any prolongation in the p1 and n1 latencies.

There is a consensus in the literature about the interpeak amplitude changes in the affected ears of BPPV patients. Yetiser et al. [2], Kim et al. [7], Lee et al. [8] and Akkuzu et al. [10] detected lower interpeak amplitudes on the affected sides of BPPV patients. In these studies, the VEMP asymmetry ratios of healthy controls were used as normalized data and compared with those of the BPPV group. On the other hand, there is no information about the comparison of mean amplitudes of BPPV patients (affected and unaffected ears) and controls in these studies. There has also been no standard approach for the evaluation of VEMP asymmetry. Yetiser et al. [2] defined asymmetry over 25% as VEMP asymmetry, although in other studies, data obtained from the control group were regarded as normative data, and VEMP asymmetry was defined as a value above an upper limit calculated by the formula [upper limit=mean of the control group+(2×standary deviation)] [7, 8, 10].

In another study, Kim et al. [7] suggested that when the amplitude of the unaffected ear is lower than that of the affected ear in BPPV, it should be accepted as a VEMP asymmetry in favor of the unaffected ear. However, this notion was not used in other studies. Moreover, in this study, significantly more VEMP abnormalities were detected in both ears of BPPV patients than in the control group.

In our study, the mean interpeak amplitudes of the affected and unaffected ears of BPPV patients did not differ from each other (p=0.467); however, both were significantly lower than the mean value of the control group (p<0.001). The mean VEMP asymmetry values of BPPV patients did not differ from those of the healthy controls, although in 12 BPPV patients, the amplitude values were lower on the unaffected side.

Our findings are valuable because we detected that the cVEMP data from the affected and unaffected ears of BPPV patients are similar. Our research correlates with that in the literature with respect to the fact that interpeak amplitudes are lower in BPPV, and it additionally reveals new information that amplitudes are lower in both ears of BPPV patients. We consider this finding to be particularly important for the assessment of BPPV etiology.

Unilateral involvement is detected by the Dix–Hallpike test or by a head-roll test in a majority of BPPV patients. It is controversial whether the primary pathology is about the structure of the otoconia or the degeneration of the neuroepithelium. Aging, diabetes mellitus, hypertension, thyroiditis, hyperlipidemia, stroke, osteoporosis, vitamin D deficiency are responsible for causing the degenerative changes of the neuroepithelial membrane, and these conditions are supposed to cause bilateral involvement [15]. Various studies have reported on the role of osteoporosis and vitamin D deficiency in the development of BPPV [4, 15-18].

Our research suggests neuroepithelial membrane involvement in both ears of unilateral BPPV patients. We think that due to this bilateral involvement, interpeak amplitude values are significantly lower in both ears of unilateral symptomatic patients. This finding supports the idea that the pathophysiological process starts with neuroepithelial membrane degeneration and continues with otoconia separation. Our research also shows that bilateral otolith dysfunction is probable in unilaterally symptomatic BPPV patients.

The major limitation of our study is that cVEMP is an indirect measurement method for vestibular end organs.

We eventually concluded that even if the symptoms of BPPV are unilateral, findings suggesting bilateral involvement of the macular neuroepithelium are important in understanding the pathophysiology of BPPV. Further research is needed to determine the VEMP characteristics of BPPV patients with comorbidities that can cause neuroepithelial degenerative changes.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Haseki Training and Research Hospital (Reference number: June-2014/S7).

**Informed Consent:** Written informed consent was obtained from patients and patients’ parents who participated in this study.
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Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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