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Otolith Dysfunction in persons with both Diabetes and Benign Paroxysmal Positional Vertigo

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Abstract

Objective—Vestibular dysfunction is a **well-recognized** complication of type 2 diabetes (DM) that may **contribute to increased fall risk.** The prevalence of benign paroxysmal positional vertigo (BPPV) is higher in people with DM. The impact of DM on the otolith organs of the vestibular system in people with BPPV is unknown. The purpose of this study was to analyze otolith function using vestibular evoked myogenic potential (VEMP) tests in people with DM and concurrent BPPV (BPPV+DM), and to examine the relationships between VEMP variables and diabetes-related variables.

Study Design—Prospective, cross-sectional study.

Setting—Tertiary academic medical center

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The authors declare no conflicts of interest.

Subjects and Methods—Participants 40-65 years, were recruited in four groups: controls (n=20), people with DM (n=19), BPPV (n=18), and BPPV+DM (n=14). Saccule and utricle function were examined using cervical VEMP (cVEMP) and ocular VEMP (oVEMP), respectively. Diabetes related variables such as HbA1c, duration of diabetes and presence of sensory impairment due to diabetes were collected.

Results—The frequency of abnormal cVEMP responses was higher in the DM (p=0.005), BPPV (p=0.003), and BPPV+DM (p<0.001) groups compared to controls. In the participants with diabetes, higher HbA1c levels were correlated with prolonged P1 (p=0.03) and N1 latencies (p=0.03). The frequency of abnormal oVEMP responses was not different between groups (p=0.2).

Conclusion—Although, BPPV and DM may independently affect utricle and saccule function, they do not appear to have a distinct cumulative effect.

Introduction

Type 2 diabetes (DM) affects 9.3% of the United States population[1] and is predicted to affect 1 in 3 people by the year 2050.[2] Diabetic complications such as peripheral neuropathy and retinopathy contribute significantly to balance deficits, increasing fall risk.[3, 4] Vestibular dysfunction may be considered another possible complication of diabetes.[5-7] In people with diabetes and vestibular dysfunction, the risk of falls increases more than two times, after adjusting for peripheral neuropathy and retinopathy.[6] Fall prevention is a major clinical focus for people with diabetes, hence examining the effect of diabetes on the vestibular system merits attention.

Animal studies have shown that diabetes affects the saccule, causing morphological changes, such as type 1 hair cell loss,[8, 9] while clinical research has shown that in people with DM, utricle and saccule function are significantly impaired compared to age matched, healthy controls.[10, 11] Degeneration of the maculae of the utricle and saccule can cause otoconia fragments to dislodge, which is the cause of one common peripheral vestibular condition, benign paroxysmal positional vertigo (BPPV).[12, 13] Recent studies have shown that BPPV is present in higher frequency in people with both type 1 and type 2 diabetes compared to healthy controls.[14-16]

Vestibular evoked myogenic potentials (VEMP) are objective, and reliable electrophysiological tests that measure otolith function.[17] The cervical VEMP (cVEMP) is a short latency muscle response believed to be of saccular origin, whereas the ocular VEMP (oVEMP) is believed to be of utricular origin.[18, 19] VEMP studies have been used to identify abnormal responses in people with BPPV, where a significantly higher frequency of abnormal cVEMP responses,[20-23] as well as oVEMP responses[24-26] are seen, compared to age matched controls. A few studies have shown VEMP abnormalities in people with diabetes.[10, 11, 27, 28] There are no studies that have examined the combined effect of BPPV and DM (BPPV+DM) on the utricle and saccule.

Given that VEMP abnormalities have been associated with both DM and BPPV independently, the primary objective of this study was to examine otolith organ function in people with BPPV+DM. We compared people with BPPV+DM to controls, people with DM

only and people with BPPV only, using VEMP testing. Our hypothesis was that the combination of the two disease processes would yield a higher frequency of abnormal VEMP responses in people with BPPV+DM compared to all other groups. A secondary aim was to examine the association between otolith dysfunction and variables that indicate severity of diabetes such as glycemic control (HbA1c), duration of diabetes, and the presence of sensory impairment due to diabetes.

Materials and Methods

Study Design

This was a single center, prospective study with a sample of convenience, conducted at a university neuro-otology clinic. The research protocol was approved by the Human Subjects Committee at the ..... All participants signed the institutionally approved written informed consent prior to participation in the study.

Participants

Participants who were 40 to 65 years of age were recruited into four groups: controls (n=20), people with type 2 diabetes without vestibular problems (DM) (n=19), people with unilateral, posterior canal BPPV canalithiasis without DM (BPPV) (n=18), and those with unilateral posterior canal BPPV canalithiasis and DM (BPPV+DM) (n=14). Our recruitment strategies included physician referral, study advertisements, and two registry programs for research participants. Participants were excluded if they had (1) a history of neurological disease including stroke, multiple sclerosis, Parkinson's disease, intracranial tumor, (2) a history of Meniere's disease, bilateral BPPV, anterior or horizontal canal BPPV, or cupulolithiasis, (3) received chemotherapy or ototoxic medications, (4) traumatic head injury, (5) conductive hearing loss. Participants with DM did not have a prior medical diagnosis of a vestibular condition, while controls did not have a recorded medical history of a vestibular disorder or DM.

The presence or absence of type 2 diabetes, hypertension, and medication list were collected by self-report from each subject, and was confirmed through electronic health records, when available. Glycosylated hemoglobin (HbA1c) via a disposable finger stick testing kit (Metrika A1cNow^{+} Bayer, Tarrytown NY) was collected. In participants with DM, history regarding duration of diabetes and history of diabetic peripheral neuropathy was collected. All participants were screened for the presence of diabetic peripheral neuropathy (DPN) using the Michigan Neuropathy Screening Instrument (MNSI).[29] Participants were classified as having DPN if their physical exam score was ≥ 2.0 (sensitivity of 65%, specificity of 83%).[29]

For participants with BPPV, inclusion was based on a diagnosis of unilateral posterior canal BPPV canalithiasis, made by a physician and confirmed by a physical therapist (LD). The diagnosis of BPPV was determined on the presence of torsional, up-beating nystagmus in the Dix-Hallpike position, which had a brief latency, and lasted less than 60 seconds, using videonystagmography (Micromedical, Visual Eyes 2002).[12]

Procedures

Participants were examined using air conducted cVEMP and oVEMP (Biologic Auditory Evoked Potentials Navigator Pro- Version 6.2.1), using self-adhesive, silver/silver chloride ECG monitoring electrodes (Tracer rite Bio-Detek Inc.). We scrubbed the skin to maintain the impedance of the recording electrodes below five kOhms. Responses to 150 sweeps were averaged and two trials were performed to verify the reproducibility of the waveform. For consistency, one investigator (LD) performed all the VEMP tests and a second evaluator (CM) confirmed absent responses.

Cervical VEMP testing (cVEMP)

The cVEMP was performed with the participant seated in an upright position. During testing, participants turned their head away from the ear being tested, while they pushed their chin against a blood pressure cuff that had been inflated to 20 mm of Hg. They were required to push against the cuff, until the pressure reached 40 mm of Hg, while watching the dial so that they could maintain the pressure, in order to monitor muscle contraction.[30, 31] The primary electrode was placed over the mid-point of the ipsilateral sternocleidomastoid muscle, the secondary on the upper forehead and ground electrode on the lower forehead. The acoustic stimulus (tone burst, 500 Hz, 95 dB HL, rate 4.3/sec, rise/fall: 2 ms, plateau: 0 ms), was delivered using insert earphones. The EMG signal was amplified (1000x), and band-pass filtered (10-1500 Hz). The first positive deflection was P1 and first negative deflection N1. Threshold was determined next by decreasing the sound volume, and noting the lowest level at which a reproducible waveform was recorded.

Ocular VEMP testing (oVEMP)

For the oVEMP, participants were sitting upright; and were instructed to maintain an upward gaze of approximately 30 degrees, on a pre-marked visual target. The primary electrode was placed below the lower lid margin of the contralateral eye, the secondary electrode above the eyebrow, and the ground at the sternum. The acoustic stimulus (tone burst, 500 Hz, 125 dB SPL, rate 5.0/sec, rise/fall: 1 ms, plateau: 2 ms), was delivered using insert earphones. The EMG signal was amplified 5000x and bandpass filtered 1-1000 Hz. The first negative deflection was n10 and first positive deflection p16.

Data Processing

Latencies of the VEMP components were defined as the time from stimulus onset to the peak of the waveform. The mean± 2 standard deviation for healthy controls was defined as the normal range of responses for the equipment and procedures used in this study. Responses were classified as abnormal if latencies were greater than this normal range, or if responses were absent. Because our equipment did not allow correction for baseline muscle activity, amplitudes of both the cVEMP and oVEMP have not been included in the analysis and results.

For participants with BPPV or BPPV+DM, the affected ear was the ear that caused symptoms of vertigo and nystagmus with the Dix-Hallpike testing. For DM and control groups, the right and left ears were both considered unaffected. After excluding absent VEMP responses, we examined differences in latency and threshold between right and left

ears and affected/unaffected ears using ANOVA. As there were no differences in latency and threshold between the right and left ears in all groups as well as between the affected/unaffected ears of participants with BPPV and BPPV+DM, data from each ear was considered as individual data points in the analysis.

Sample size determination

Significant differences have been noted in cVEMP latencies between controls p13 (13.25 ± 0.93 ms), n23 (22.62 ± 1.76 ms) compared to people with BPPV p13 (14.99 ± 1.89 ms) and n23 (24.31 ± 2.26 ms).[23] Likewise, significant differences in cVEMP latency were noted between controls p13 (15.1± 0.7 ms), n23 (24.6 ±1.1 ms) compared to people with DM p13 (16.9 ±1.6 ms), n23 (26.7 ±1.9 ms).[11] Based on these studies the effect size calculated is 0.9, which is a large effect size. However, because our group of interest was the BPPV+DM group, and there are no studies that have compared BPPV+DM group with the BPPV or DM groups, we assumed a small effect size. To achieve 80% power, we required a total sample size of 80, with significance set at 0.05, with 20 participants in each group.

Statistical Analysis

Descriptive statistics (mean, standard deviation, %) were used to examine participant demographics. Group differences in participant demographics were tested using ANOVA, and Tukey's procedures for post-hoc comparisons between groups for significant variables. Chi-square tests were used to determine differences in the frequency of abnormal responses between groups. Differences in HbA1c and duration of diabetes between participants with normal responses and those with abnormal responses in the diabetes groups were examined using ANOVA. After excluding absent VEMP responses, we examined the VEMP responses for normality and equality of variances, and compared them across groups using ANOVA for normally distributed variables and Kruskal-Wallis test for n10 and p16 latency of oVEMP. In the two groups of participants with diabetes (DM and BPPV+DM), the relationship between age, sex, BMI, hypertension, HbA1c, years with DM, and MNSI scores and cVEMP and oVEMP variables were examined using multiple linear regression. A p-value <0.05 was considered statistically significant. We used SPSS for Windows version 20.0 (SPSS Inc., Chicago, USA).

Results

Seventy-one individuals participated in the study in four groups: controls (n=20), DM (n=19), BPPV (n=18) and BPPV+DM (n=14). HbA1c, BMI, and the prevalence of hypertension were significantly higher in the groups with diabetes (Table 1).

Frequency of abnormal VEMP responses

cVEMP responses—In the control group, thirty-eight ears showed a normal cVEMP response. The normal range for P1 latency (mean±2SD) was 13.5-19.4ms, and N1 latency was 21.8-27.52ms. Based on these findings, the P1 and N1 responses in all four groups were classified as normal, delayed, or absent. We observed significant differences in the frequency of abnormal responses between the DM, BPPV and BPPV+DM groups, when compared to

controls (p<0.01) (Table 2). There were no differences in the frequency of abnormal responses between any of the other groups (DM, BPPV, and BPPV+DM).

In the two diabetes groups examined (DM and BPPV+DM, n=33), 15 participants had absent or delayed responses (45.5%), in at least one ear. In these participants, the mean HbA1c was 8.3 ± 1.7% compared to 6.8 ± 1.2% in participants with normal responses (p=0.006); the mean duration of diabetes was 8.0 ± 10.2 years compared to 4.7 ± 6.2 years in those with normal responses (p=0.27). Figure 1 illustrates the cVEMP responses of a participant in each group.

oVEMP responses—In the control group, thirty-four ears showed a normal oVEMP response. The normal range for n10 latency was 8.6-13.3ms and p16 latency was 14.0-18.7ms. No differences were noted in the frequency of abnormal responses between any groups (p=0.2) (Table 3).

In the two groups of participants with diabetes (DM and BPPV+DM, n=33), 17 had delayed or absent oVEMP responses (51.5%), in at least one ear. The mean HbA1c in these participants was 8.0 ± 1.8% compared to 6.9 ± 1.2% (p=0.06); mean duration of diabetes was 7.9 ± 9.6 years compared to 4.4 ± 6.4 years, in participants with normal responses (p=0.24). Figure 2 illustrates the oVEMP responses of a participant in each group.

Comparison of VEMP variables across groups—Analysis of present responses showed no differences in the cVEMP P1 and N1 latency, or threshold between the four groups. Significant differences were found in oVEMP n10 latency between groups (p=0.03); post hoc tests showed that the DM group had prolonged n10 latency compared to controls.

Relationships between VEMP variables and diabetes variables

cVEMP variables: In the two groups of participants with diabetes (DM and BPPV+DM, n=56 ears with responses), we examined the relationship between age, sex, BMI, HbA1c, hypertension, MNSI physical score, years with diabetes and cVEMP variables. P1 latency (r=0.44) was associated with BMI (p=0.001) and HbA1c level (p=0.05), while N1 latency (r=0.5) was associated with HbA1c level (p=0.01). Threshold (r=0.49), was associated with HbA1c level (p=0.04) and MNSI physical score (p=0.003).

oVEMP variables: In the diabetes groups (DM and BPPV+DM, n= 51 ears with responses), we examined the relationship between age, sex, BMI, HbA1c, hypertension, MNSI physical scores, years with diabetes, and oVEMP variables. No associations were seen between the latency of oVEMP (r=0.61) and diabetes variables.

Discussion

The results of this study reveal a higher prevalence of abnormal cervical VEMP responses in people with DM, BPPV, and both BPPV+DM as compared to controls of similar age. Contrary to our hypothesis, people with BPPV+DM did not have a higher frequency of abnormal cVEMP responses compared to people with either DM only or BPPV only. The frequency of abnormal cVEMP responses in BPPV (30.6%) is similar to observations made

by others.[21, 22] After excluding absent VEMP responses from the analysis, we found no differences in latency or threshold between the groups. This finding differs from Hong et al[20] who found that 75% of their participants with BPPV had prolonged P1 latencies, compared to healthy controls. This difference may be due to the wide age range of participants recruited for their study (20 to 81 years); advancing age is associated with prolonged VEMP latencies.[32]

Our findings of a 28.9% abnormal cVEMP response rate in people with DM are similar to other studies,[10, 11] however, we did not see prolonged latencies or reduced amplitude when we compared people with diabetes to our control group. The main difference between this study, and the one by Ward et al,[10] is that their participants were older with a 10-year or longer history of DM. We did see a relationship between prolonged latency of P1 and N1 with higher HbA1c levels.

When participants with DM and BPPV+DM were examined, we found that 45.5% had absent or delayed responses, with a significantly higher HbA1c level in people with abnormal responses. Degeneration of the macula of the saccule, is one suggested cause for detachment of the otoconia, causing BPPV,[20, 22] while degeneration of the vestibulocochlear nerve; particularly the inferior vestibular nerve has been observed in BPPV.[33] These pathophysiological mechanisms of damage have been seen in experimentally induced diabetic rats, where histopathological changes were proposed to be due to metabolic stress.[9] Diabetic rats have been shown to have myelin sheath abnormalities of the vestibulocochlear nerve which may be due to non-enzymatic glycosylation of myelin protein.[8] These morphological changes may explain both delayed and absent VEMP responses.

Our study did not find a difference in abnormal cVEMP responses between the DM, BPPV, and BPPV+DM groups. This finding is interesting because the individuals with DM did not have a diagnosis of vestibular disease. Other researchers have noted a higher frequency of vestibular dysfunction in people with diabetes, who are asymptomatic, compared to healthy controls.[34, 35] Gawron et al[35] found a higher frequency of spontaneous and positional nystagmus in children with type 1 diabetes, however, only 6.3% of their participants complained of vertigo, imbalance, or both. Likewise, even though vestibular dysfunction was evident with VEMP testing, Konukseven et al[11] reported no complaints of dizziness in 70% of people with DM. People with diabetes may have symmetrical involvement of both inner ears with minimal complaints of dizziness, and clinical symptoms may be seen only when damage to the vestibular system is severe.[36]

Analysis of the oVEMP showed no differences in the frequency of abnormal oVEMP responses between any groups. This was surprising since utricle dysfunction is prevalent in people with BPPV,[24, 26] Nakahara et al[24] found that 66.7% of ears affected with BPPV had abnormal responses compared to age-matched controls. However, their study participants belonged to a wide age range (34 to 82 years), and they reported amplitude of the oVEMP when they examined the frequency of abnormal responses. We classified abnormal responses based on the latency of the oVEMP only, because the equipment we used did not have the electromyography capability to correct for baseline variations in ocular muscle activity. However, comparisons of oVEMP latency across groups showed significantly prolonged n10

latency in the DM group compared to controls. Our results are similar to two recent studies that have examined the oVEMP in people with DM showing prolonged latency of n10[10, 11] compared to healthy, age matched controls.

We did not find associations between oVEMP and diabetes variables in participants with DM and those with BPPV+DM. DM did not appear to affect the utricle as clearly as it did saccule, a result that is supported by a recent study by Konukseven et al,[11] who speculated that hyperglycemia may not affect the superior vestibular nerve.

One limitation of this study is the small sample size, and the exclusion of missing data when we compared variables between groups. However, because of the strict inclusion criteria, we were able to focus our attention to people with BPPV in a single canal. Because of the cross-sectional nature of this study, we cannot determine the causal relationship between diabetes and vestibular dysfunction in people with BPPV. We did not perform a neurootologic examination of the healthy controls and people with DM only. Although their medical records did not indicate vestibular disease, they could have had subtle vestibular deficits. We did not analyze amplitudes of the VEMP due to inability to correct for baseline variation in muscle activity.

Ultimately, the interest in examining otolith function is to determine how this finding may affect a person's mobility and balance. People with BPPV have been shown to have otolith organ dysfunction,[21, 24] and otolith dysfunction is associated with postural instability and higher risk for falls.[37, 38] People with diabetes are prone to developing diabetic complications, of which peripheral neuropathy and retinopathy increase the risk of falls.[3, 4, 39] Understanding the impact of multiple sensory deficits, and their relative contribution to fall risk, could help in developing strategies to prevent falls. Future studies examining the incidence of falls in people with BPPV+DM who have abnormal VEMP responses, will elucidate the relationship between otolith dysfunction and falls.

Conclusion

This study showed that both adults with BPPV and those with DM have otolith dysfunction; indicating that BPPV and DM may independently affect utricle and saccule function; however, they do not appear to have a distinct cumulative effect.

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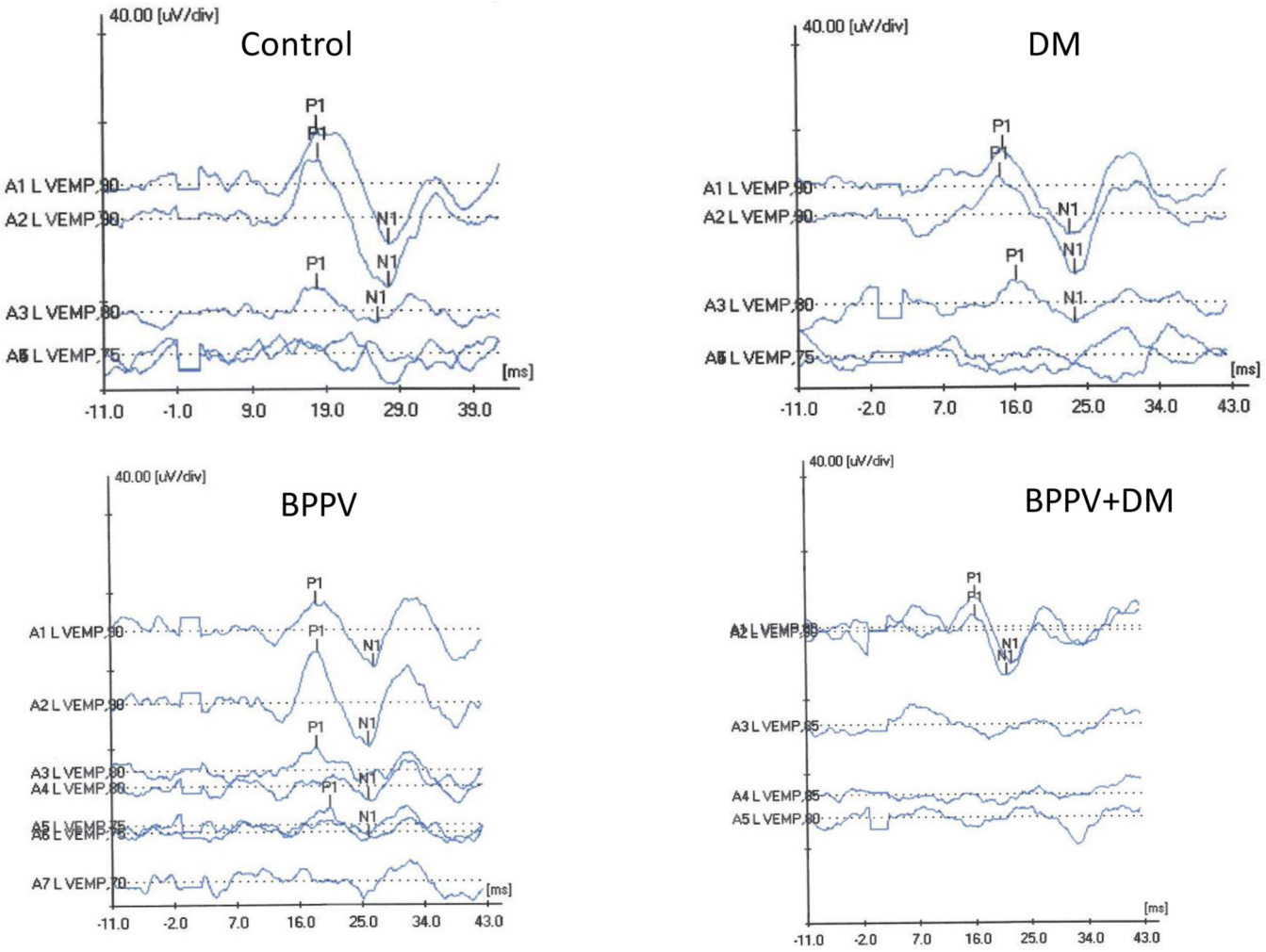

Figure 1. Tracings of the cVEMP responses in the left ear of four participants, one from each group, matched by age and gender

Controls, DM- type 2 diabetes, BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and diabetes

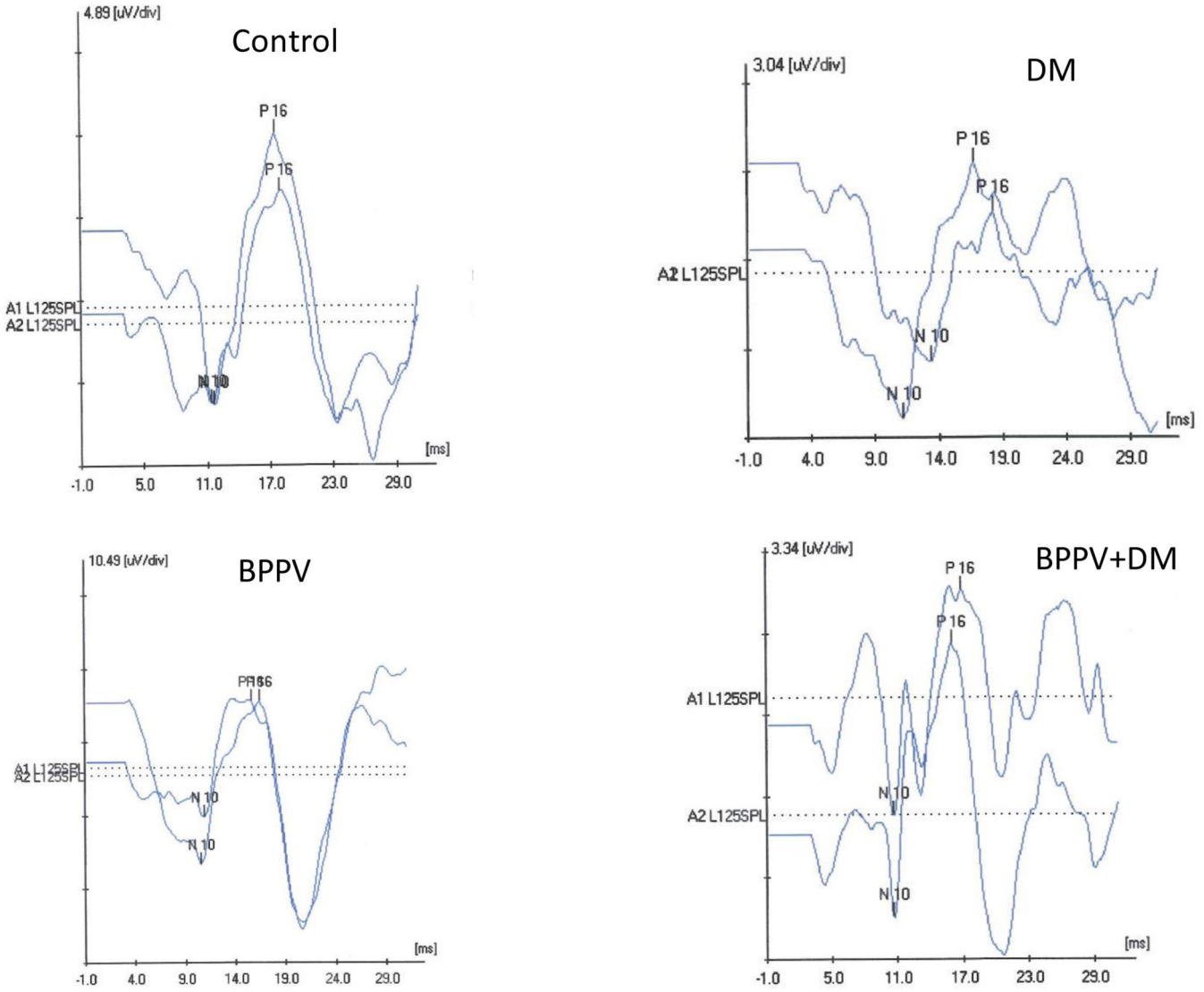

Figure 2. Tracings of the oVEMP responses in the left ear of four participants, one from each group, matched by age and gender

Controls, DM- type 2 diabetes, BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and diabetes

Table 1

Demographics of the groups

	Control (n=20)	T2D (n=19)	BPPV (n=18)	BPPV+DM (n=14)	p-value
Age (years)	57.5 ± 5.3	58.6 ± 5.3	54.9 ± 5.9	58.5 ± 5.6	p=0.17
Gender (M/F)	6/14	5/14	4/14	5/9	p=0.84
HbAlc (unit-%)	5.3 ± 0.3	7.8 ± 1.7	5.6 ± 0.4	7.1 ± 1.5	p<0.01 *
BMI (kg/m^2)	26.9 ± 5.3	35.4 ± 6.3	29.5 ± 8.1	37.4 ± 5.2	p<0.01 *
Hypertension (%)	5 (25%)	13 (65%)	8 (44.4%)	13 (92.9%)	p<0.01 *
Diabetic peripheral neuropathy	-	11 (58%)		7 (50%)	
Years with T2D	-	10 ± 8.8	-	10.6 ± 11	

HbA1c= glycosylated hemoglobin, BMI= body mass index. Continuous variables are described as mean ± SD, categorical variables as count (percentages).

* p values are based on chi square tests for frequencies and ANOVA for continuous variables.

Table 2

Frequency of abnormal cVEMP responses in each group

	P1 delay	N1 delay	P1 and N1 delay	cVEMP not recordable	cVEMP abnormal
Control (n= 40 ears)	1	0	0	1	2 (5%)
Type 2 diabetes (n= 38 ears)	3	3	0	5	11 (28.9%) p=0.005 *
BPPV (n=36 ears)	1		3		11 (30.6%) p=0.003 *
BPPV+DM (n=28 ears)	2	1	3	5	11 (39%) p<0.001 *

chi square tests were conducted.

* Significant differences between controls and the three other groups noted. BPPV- benign paroxysmal positional vertigo, BPPV+DM- BPPV and type 2 diabetes

Table 3

Frequency of abnormal oVEMP responses in each group

	n10 delay	p16 delay	n10 and p16 delay	oVEMP not recordable	oVEMP abnormal
Control (n= 40 ears)	1	1	0	4	6 (15%)
Type 2 diabetes (n= 38 ears)	2	1	1	9	13 (34%) (p=0.05)
BPPV (n=36 ears)	0	0	2	10	12 (33%) (p=0.06)
BPPV+DM (n=28 ears)	3	0	0	6	9 (32%) (p=0.08)

Chi-square tests were used to compare frequency of abnormal responses across groups. BPPV-benign paroxysmal positional vertigo, BPPV+DM-BPPV and type 2 diabetes