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OTOLOGY

Idiopathic latent vestibulopathy: a clinical entity as a cause of chronic postural instability

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Abstract The objective of this study is to describe a new clinical entity of idiopathic latent vestibulopathy (ILV), in which patients have unilateral or bilateral vestibulopathy combined with unsteadiness but without episodic vertigo, auditory disturbance, or a medical history suggesting the presence of vestibulopathy. A retrospective study of 1,233 consecutive new outpatients was conducted. Two-legged stance tasks were performed by 11 patients identified as having ILV in four conditions: eyes open with and without foam rubber, and eyes closed with and without foam rubber. We examined six parameters: the velocity of movement of the center of pressure (COP) with eyes closed/foam rubber, the envelopment area traced by the movement of the COP with eyes closed/foam rubber, Romberg's ratio of velocity and area with foam rubber, and the foam ratios of velocity and area with eyes closed. Multiple regression analyses were performed in order to explore the relationship between the presence of ILV and the six parameters recorded during foam posturography, while adjusting for the subjects' gender and age. The presence of ILV had a significantly positive relationship with the values of 4 of the 6 parameters. Even though six patients showed only unilateral vestibulopathy, their median value in all 6 parameters was greater than that of healthy controls. ILV could be a clinical entity accountable for postural instability.

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Introduction

Unsteadiness, which is defined as the feeling of being unstable while seated, standing, or walking without a particular directional preference, can occur in many pathological conditions including peripheral vestibulopathy [1]. If unsteadiness is present without episodic vertigo, auditory disturbance, or a medical history suggestive of vestibulopathy, such as exposure to ototoxic drugs, clinicians usually consider peripheral vestibular disorders to be unlikely.

However, detailed vestibular examinations revealed that a portion of such patients have peripheral vestibular dysfunction [2, 3]. It is known that bilateral vestibulopathy (BV) causes persistent imbalance, especially in darkness. Previous articles have reported acquired, cryptogenic BV in the absence of any auditory disturbance other than presbycusis as idiopathic bilateral vestibulopathy (IBV) [2, 3]. Some IBV patients have chronic unsteadiness without episodic vertigo. They have been classified as a slowly progressive type of IBV, in which bilateral vestibular function deteriorates gradually [2, 3]. On the other hand, there has been little discussion as to whether unilateral vestibulopathy (UV) without episodic vertigo, auditory disturbance, or a history suggesting vestibular disorders can be responsible for the symptom of unsteadiness. In vestibular neuritis, a disease showing idiopathic UV with a single vertigo attack, recovery from the symptoms stems from both recovery of peripheral vestibular function and from vestibular compensation [4, 5]. Even at the chronic stage following acute unilateral vestibular damage, patients who complain of unsteadiness are still present in considerable numbers [6, 7]. We previously reported that postural instability following acute UV remained even at the chronic stage, if the unilateral vestibular dysfunction was still severe [8]. Therefore, we hypothesized that UV as well as BV could account for the postural instability of patients who complain of unsteadiness without any other symptoms or histories suggesting vestibular disorders. We identified these patients as having idiopathic latent vestibulopathy (ILV).

The purpose of this study was to assess the static postural equilibrium abilities in patients with ILV complaining of unsteadiness but without episodic vertigo. We examined the clinical manifestations of ILV and assessed the postural stability of patients with ILV using a foam posturography analysis system, of which the diagnostic accuracy for peripheral vestibular disorders has been demonstrated in accordance with the guidelines from the standards for reporting of diagnostic accuracy initiative [9–11].

Patients and methods

Study design

This observational case series study was approved by the regional ethical standards committee in the Faculty of Medicine at the University of Tokyo and conducted according to the tenets of the Declaration of Helsinki. This study is reported in accordance with the guidelines from Strengthening the Reporting of Observational Studies in Epidemiology for the reporting of observational research [12].

Patients

We reviewed the clinical records of 1,233 consecutive new patients visiting the Balance Disorder Clinic at the University of Tokyo Hospital between December 2006 and September 2010. Of these, 827 patients underwent both caloric testing and cervical vestibular evoked myogenic potential (cVEMP) testing. All of these patients received a detailed history-taking and a battery of tests including a physical examination and standardized neurological, neuro-otological, neuro-ophthalmological and audiological examinations. Eye movements were observed using an infrared charge-coupled device camera and recorded by electronystagmography.

Diagnostic criteria for bilateral ILV were: (1) showing unsteadiness, (2) no episodic vertigo/dizziness, (3) no medical history of, or suggestion of, a psychogenic disorder, (4) no medical history of other neurological disorders, (5) no familial history of auditory or vestibular dysfunction, (6) no past history of excessive noise exposure, head injury or exposure to ototoxic drugs, (7) abnormal caloric responses bilaterally and/or bilaterally absent cVEMP responses to short tone burst stimulation, (8) no sensorineural hearing loss except for presbycusis, (9) no abnormal findings on standard neurological examinations except for vestibular dysfunction, and (10) no abnormal findings in magnetic resonance imaging of the brain, the ear and the cerebellopontine angle.

For unilateral ILV, the same criteria were used, except for criterion (7) in which abnormal caloric responses and/or abnormal cVEMP responses were observed unilaterally.

We recruited 66 healthy control subjects [22 men, 44 women, mean (±SD) age 56.5 (±14.6) years, range 24–79], who were the same group used in our previous report [11].

Caloric test

Caloric testing, which has been used as a clinical test of the lateral semicircular canal and superior vestibular nerve systems, was performed as reference standard by irrigating the external auditory canal with 2 ml ice water for 20 s followed by aspiration of water in a darkened room. This method of caloric stimulation is easier to perform than bithermal irrigation with water at 30 and 44 °C, and has been shown to have a high sensitivity and specificity for detecting canal paresis (CP) based on Jonkees' formula [13]. Caloric nystagmus was recorded using an electronystagmograph. CP was calculated as the difference between the maximal slow phase eye velocity (MSPV) for each ear divided by the sum of the slow phase eye velocities. An abnormal caloric response was defined by either of the following criteria: (1) a CP percentage of 20 % or more; (2) a MSPV in both ears of 10°/s or less [11].

cVEMP test

cVEMP testing has been used as a clinical test of the saccule and inferior vestibular nerve system, since previous studies have suggested that these responses are generated by the activation of saccular afferents [14–17]. Electromyographic (EMG) activity was recorded from a surface electrode placed on the upper half of each sternocleidomastoid muscle (SCM), with a reference electrode on the side of the upper sternum and a ground electrode on the nasion. During the recording, subjects in the supine position were instructed to raise their heads from the pillow in order to contract the SCM. The overall EMG activity of the SCM was set as the reference level of the tonic contraction. During the recording, EMG activity was monitored on a display in order to ensure that muscle activity was maintained at a sufficient level (EMG activity >150 μV) in each patient. The EMG signal from the stimulated side was amplified and bandpass filtered (20–2,000 Hz). The stimulation rate was 5 Hz, and the time window for analysis was 100 ms. Short tone bursts of 500 Hz (95 dB nHL (equivalent to 135 dB SPL); rise/fall time 1 ms; plateau time 2 ms) were presented to each ear through headphones (Type DR-531, Elega Acous. Co. Ltd., Tokyo, Japan). The latencies and amplitudes of the first positive–negative peaks (p13–n23) of the VEMP were evaluated from the average of two runs. The absence of reproducible p13–n23 peaks in two runs was regarded as an absent cVEMP response. For the evaluation of the amplitude, the percentage of cVEMP asymmetry (cVA) was calculated as 100[(Au − Aa)/(Aa + Au)], where Au is the p13–n23 amplitude on the unaffected side and Aa is the p13–n23 amplitude on the affected side [18]. On the basis of results from normal subjects in a previous study, the upper limit of percentage of cVA was set as 34.0 [19]. Subjects with an air-bone gap (more than 10 dB) [20], or difficulty in maintaining SCM activity at a sufficient level during cVEMP recordings, were not enrolled in this study. A percentage of cVA above the upper limit was regarded as unilaterally abnormal cVEMP responses. Absent cVEMP responses on both sides were regarded as bilaterally abnormal cVEMP responses.

Foam posturography

We used a Gravicorder G-5500 (Anima Co. Ltd., Tokyo, Japan) with/without a foam rubber (Nagashima Medical Instruments, Tokyo, Japan) containing vertical force transducers to determine instantaneous fluctuations in the center of pressure (COP) at a sampling frequency of 20 Hz [11]. The sway path of the COP was obtained from these data. Two-legged stance tasks were performed under four conditions: eyes open or eyes closed, with or without the foam rubber. The distal ends of the big toes of the feet were positioned 45° apart with the heels of both feet close to each other. The recording time was 60 s or until the subject required assistance to prevent falling. In the eyes-open condition, the subjects were asked to watch a small red circle 2 m away from where they were standing in a quiet, well-lit room. The 2 outcome measures were: the mean velocity of movement of the COP over 60 s, which was termed "velocity", and the envelopment area traced by the movement of the COP, which was termed "area". We calculated Romberg's ratio for both velocity and area, with and without the foam rubber. Romberg's ratio is defined as the ratio of a measured value with the eyes closed to that with the eyes open. We additionally defined the "foam ratio" as the ratio of a measured value with the foam rubber to that without the foam rubber. We calculated the foam ratio of the velocity and the area, with the eyes open and closed. Any increase in body sway measured while standing on foam rubber with the eyes closed is considered specific to vestibular disorders, because, under these conditions, the role of vestibular inputs becomes more pronounced while visual and somatosensory inputs are reduced. Romberg's ratio and the foam ratio may reflect visual and somatosensory dependence, respectively, in maintaining an upright posture. This is based on the principle that standing with the eyes closed and standing on a foam surface alter visual and somatosensory information, respectively.

We previously revealed that the following six parameters showed significantly higher values ($p < 0.001$) in patients who showed abnormal caloric responses in one or both ears: (1) the velocity with eyes closed/foam rubber, (2) the area with eyes closed/foam rubber, (3) Romberg's ratio of the velocity with foam rubber, (4) Romberg's ratio of the area with foam rubber, (5) the foam ratio of the velocity with eyes closed and (6) the foam ratio of the area with eyes closed [11]. We adopted these six parameters for investigation in this study.

Statistical methods

Multiple regression analyses were performed in order to explore the relationship between the presence of ILV and the six parameters recorded during foam posturography, while adjusting for the subjects' gender and age. The independent variables were gender (male = 1, female = 0), age (range 24–79 years), and the presence of ILV (yes = 1, no = 0). In the multiple regression analyses, subjects who required intervention to prevent them falling had their values set to be the same as the maximal values recorded by subjects who were able to stand unaided for the 60 s duration of the trial.

The Wilcoxon rank sum test was performed in order to investigate the difference in the values of the six parameters between patients with unilateral and bilateral ILV. Subjects who required intervention to prevent them falling were attributed a value above the maximum value obtained from subjects who were able to stand unaided for 60 s. For example, the maximum value of Romberg's ratio of velocity recorded in a subject who was able to stand throughout the test was 4.07. Hence, subjects who required intervention were given a value of 5.00. All of the parameters were regarded as ordinal parameters in the Wilcoxon rank sum test.

Statistical analyses were calculated using SPSS version 11.0J (SPSS Japan Inc., Tokyo, Japan).

Results

Clinical manifestation and findings in ILV

Of the 827 outpatients, 11 patients [1.3 %; 6 men, 5 women; mean (±SD) age, 60.5 (±15.1) years; range 34–79] were diagnosed as having ILV. The 11 ILV patients constituted 2.0 % of 555 patients diagnosed with peripheral vestibulopathy (67.1 % of the 827 patients).

Out of these patients, 6 patients [0.7 % of 827 patients; 4 men, 2 women; mean (±SD) age, 56.2 (±18.8) years; range 34–79] were unilateral ILV (Table 1), which constituted 1.6 % of the 382 patients with UV (46.2 % of the 827 patients). These 6 patients had the feeling of being unstable while standing or walking without any known cause. They had not experienced episodic vertigo/dizziness, and did not complain of hearing loss or tinnitus. Two patients (33.3 % of 6 unilateral ILV) showed spontaneous nystagmus toward the unaffected side with eyes open in the dark whereas no patients showed gaze-evoked nystagmus. Three patients (50.0 % of unilateral ILV) showed unilateral abnormal caloric responses in the presence of normal cVEMP responses. Two patients (33.3 % of unilateral ILV) showed unilateral abnormal cVEMP responses in the presence of normal caloric responses. Only one patient (16.7 % of unilateral ILV) showed unilateral abnormal findings in both caloric and cVEMP testing.

The other 5 patients [0.6 % of 827 patients; 2 men, 3 women; mean (±SD) age, 65.8 (±8.1) years; range 58–78] were bilateral ILV (Table 1). These 5 bilateral ILV patients constituted 2.9 % of 173 patients with BV (20.9 % of the 827 patients). Similarly to unilateral ILV patients, they complained of being unstable while standing or walking without any known cause. They had not experienced episodic vertigo/dizziness, and did not complain of hearing loss or tinnitus. None showed gaze-evoked or spontaneous nystagmus. Three patients (60.0 % of bilateral ILV patients) showed no VEMP responses on either side, as well as reduced caloric responses bilaterally whereas one patient showed normal cVEMP responses on both sides. The final patient showed no cVEMP responses on either side in the presence of bilateral normal caloric responses.

Posturographic findings in ILV patients

All 11 patients diagnosed with ILV underwent foam posturography testing on the same day as the caloric and cVEMP testing during their first visit to our clinic. Multiple regression analyses revealed that the presence of ILV is significantly positively related to the values of the following four parameters after adjusting for the subjects' gender and age: the velocity with eyes closed/foam rubber, the area with eyes closed/foam rubber, Romberg's ratio of the velocity with foam rubber and Romberg's ratio of the area with foam rubber (Fig. 1; Table 2, see Supplementary Table S1 for detail).

We investigated the value of all six parameters in unilateral and bilateral ILV patients independently. One bilateral ILV patient required assistance to prevent falling in the eyes closed/foam rubber condition whereas no patients with unilateral ILV required assistance during the test (Fig. 2). No significant differences were found in the 6 parameters between unilateral and bilateral ILV using the Wilcoxon rank sum test (Table 3). The median values of all 4 parameters in which there were significant differences between ILV patients and healthy controls were greater in both unilateral ILV and bilateral ILV patients than in healthy controls. The median values of the other two

Table 1 Clinical features of ILV patients

Age/sex	Duration from onset of the first symptoms	Nystagmus	Caloric test	cVEMP (short tone burst)
Unilateral ILV				
34/M	2 months	Spontaneous (leftward)	Rt. CP100 %	Rt. no responses
42/F	1.5 months	No	Lt. CP34 %	Normal
43/M	7 months	Spontaneous (rightward)	Lt. CP100 %	Normal
66/M	2 months	No	Rt. CP71 %	Normal
73/F	1 month	No	Normal	Rt. hyporesponsiveness
79/M	8 months	No	Normal	Rt. hyporesponsiveness
Bilateral ILV				
58/F	10 years	No	Bil. hyporesponsiveness	Normal
59/M	4 years	No	Bil. hyporesponsiveness	Bil. no responses
66/M	2 months	No	Bil. hyporesponsiveness	Bil. no responses
68/F	3 years	No	Bil. hyporesponsiveness	Bil. no responses
78/F	4 years	No	Normal	Bil. no responses

ILV idiopathic latent vestibulopathy, *cVEMP* cervical vestibular evoked myogenic potential, *CP* canal paresis, *Rt.* right, *Lt.* left, *Bil.* bilateral

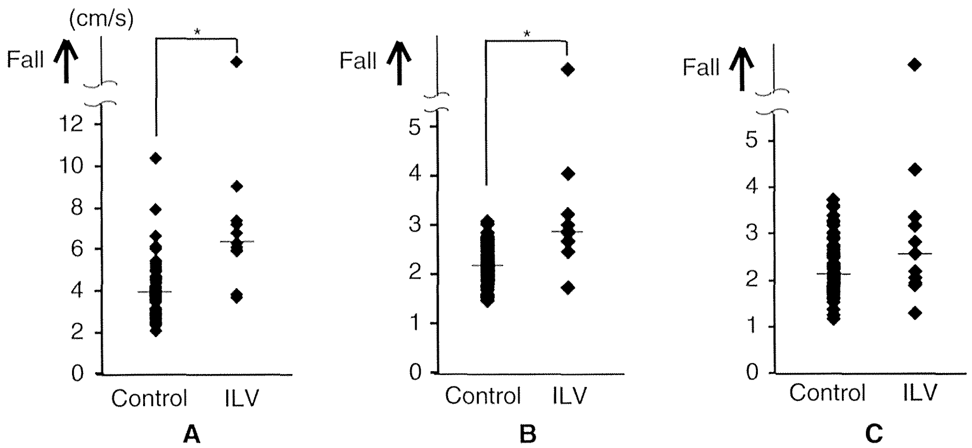

Fig. 1 *Dot plots* of parameters associated with the velocity in control subjects and patients with ILV. **a** Velocity with eyes closed/foam rubber. **b** Romberg's ratio of the velocity with the foam rubber. **c** Foam ratio of the velocity with the eyes closed. The *dots* above the undulating *lines* represent the data of subjects who required assistance to prevent falling. The *horizontal lines* represent median values. Out of the three parameters, the presence of ILV is significantly positively related to the values of the velocity with eyes closed/foam rubber and Romberg's ratio of the velocity with the foam rubber after adjusting for the subjects' gender and age (*$p < 0.001$, see Supplementary Table S1 for detail). *ILV* idiopathic latent vestibulopathy

Table 2 Values of the 6 variables in normal healthy controls and ILV patients

	Posturography	Eyes	Median (IQR)		*p* value
			Control ($n = 66$)	ILV ($n = 11$)	
Velocity (cm/s)	Foam	Closed	3.90 (2.86–4.52)	6.22 (5.83–7.30)	<0.001
Area (cm^2)	Foam	Closed	14.57 (10.07–19.99)	29.49 (20.52–41.96)	<0.001
Romberg's ratio of velocity	Foam		2.20 (1.97–2.48)	2.88 (2.68–3.24)	<0.001
Romberg's ratio of area	Foam		3.48 (2.36–4.23)	5.91 (3.20–7.65)	<0.001
Foam ratio of velocity		Closed	2.20 (1.94–2.72)	2.58 (1.95–3.37)	0.07
Foam ratio of area		Closed	3.49 (2.67–5.02)	3.53 (3.13–7.80)	0.14

The *p* value was calculated by multiple regression analysis between ILV patients and healthy controls, adjusting for the subjects' gender and age (see Supplementary Table S1 for detail)

ILV idiopathic latent vestibulopathy, *IQR* interquartile range

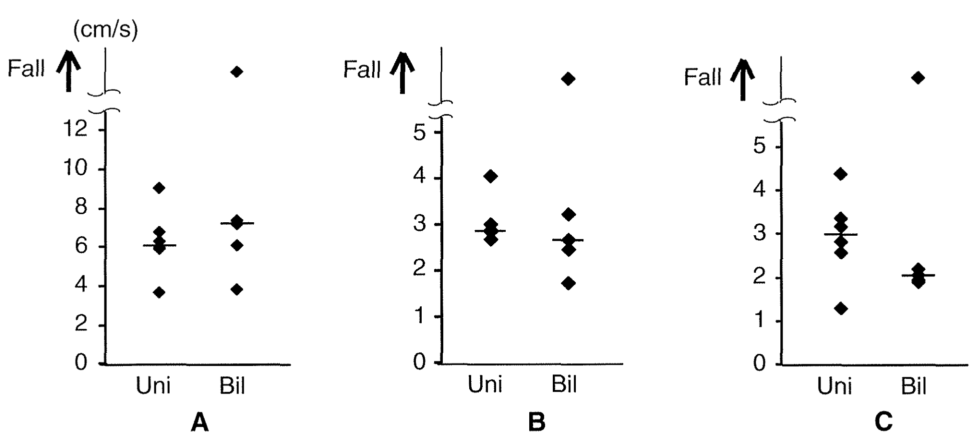

Fig. 2 *Dot plots* of parameters associated with the velocity in patients with unilateral and bilateral ILV. **a** Velocity with eyes closed/foam rubber. **b** Romberg's ratio of the velocity with the foam rubber. **c** Foam ratio of the velocity with the eyes closed. The *dots* above the undulating *lines* represent the data of subjects who required assistance to prevent falling. The *horizontal lines* represent median values. No significant differences were found in the six parameters between unilateral and bilateral ILV patients, using the Wilcoxon rank sum test ($p > 0.05$). *Unilat* unilateral ILV, *Bilat* bilateral ILV

Table 3 Values of the six variables in the unilateral and bilateral ILV patients

	Posturography	Eyes	Median (IQR)		*p* value
			Unilateral ILV ($n = 6$)	Bilateral ILV ($n = 5$)	
Velocity (cm/s)	Foam	Closed	6.04 (5.27–7.26)	7.11 (4.89-fall)	0.43
Area (cm^2)	Foam	Closed	32.50 (19.20–48.96)	28.78 (17.97-fall)	0.79
Romberg's ratio of velocity	Foam		2.89 (2.82–3.28)	2.68 (2.40-fall)	0.54
Romberg's ratio of area	Foam		6.26 (3.97–8.08)	5.91 (2.62-fall)	0.93
Foam ratio of velocity		Closed	3.01 (2.26–3.63)	2.06 (1.93-fall)	0.43
Foam ratio of area		Closed	5.12 (2.81–8.96)	3.53 (2.90-fall)	1.00

20 % of the patients with bilateral ILV required assistance to prevent falling. The 75 percentile of patients with mixed type bilateral ILV could not be specified for any of the variables due to falls by these patients. The *p* value was calculated using the Wilcoxon rank sum test between unilateral and bilateral ILV patients

ILV idiopathic latent vestibulopathy, *IQR* interquartile range

parameters, the foam ratio of the velocity with eyes closed and the foam ratio of the area with eyes closed, were greater in unilateral ILV than in healthy controls.

Discussion

ILV was identified in 11 patients, constituting 2.0 % of patients with peripheral vestibulopathy. In foam posturography testing, the presence of ILV had a significantly positive relationship relative to healthy control subjects in the following four parameters: the velocity with eyes closed/foam rubber, the area with eyes closed/foam rubber, Romberg's ratio of velocity with foam rubber and Romberg's ratio of area with foam rubber. There were no significant differences in the values of any of the six parameters tested between patients with unilateral (six patients) or bilateral (five patients) ILV. Even though the six unilateral ILV patients showed only unilateral vestibular dysfunction, the median value of all six parameters was greater in these patients than in healthy controls.

Patients with ILV accounted for only 2.0 % of patients with peripheral vestibulopathy, supporting the conventional view that a vestibular disorder is unlikely when patients complain of unsteadiness without episodic vertigo or auditory disturbance, and do not have a medical history suggestive of vestibulopathy. However, this study demonstrates that ILV can nevertheless cause postural instability. In foam posturography testing, there were significant differences in the velocity and area with eyes closed/foam rubber between ILV patients and healthy control subjects. These measures might reflect peripheral vestibular function indirectly, because the visual and somatosensory inputs were reduced in this condition.

A gradual loss of vestibular function commonly occurs in patients with vestibular schwannoma. It has been reported that the incidence of episodic vertigo is low in vestibular schwannoma, whilst complaints of unsteadiness are relatively high [21, 22], a similar finding to the symptoms reported by unilateral ILV patients. Although unilateral ILV patients did not complain of vertigo, 2 of the 6 unilateral ILV patients showed spontaneous nystagmus toward the unaffected side with eyes open in the dark in this study. This may have been due to inadequate vestibular compensation.

Romberg's ratio of velocity and area with foam rubber, which reflects visual dependence, was significantly greater in ILV patients in comparison with healthy controls. On the other hand, the foam ratio of velocity and area with the eyes closed, which reflects somatosensory dependence, was not significantly different between ILV patients and controls. The reason for this discrepancy is uncertain. In unilateral ILV, the median values of the foam ratio of velocity and area with eyes closed were both relatively high. Therefore, visual dependence is high in both unilateral and bilateral ILV but somatosensory dependence is high in only unilateral ILV. This finding may be caused by differences in the sensory strategies used for postural control between unilateral ILV and bilateral ILV patients. Another possibility is that Romberg's ratio may be better than the foam ratio in the detection of patients with peripheral vestibulopathy. Using the same posturography system, our group previously demonstrated that Romberg's ratios of velocity and area with foam rubber were more sensitive than the foam ratios of velocity and area with eyes closed for diagnosing peripheral vestibulopathy with abnormal caloric responses [11].

We did not assess the function of the vertical semicircular canals and the utricle in this study. Using the vestibular function tests that can assess these vestibular end organs such as a head thrust test or ocular VEMPs, more ILV patients might be detected. Further study is needed to identify specific clinical features of ILV.

We report that while unilateral or bilateral ILV constitute a small proportion of patients with vestibulopathy, they are both a significant cause of postural instability. We advocate that ILV could be a clinical condition accountable for postural instability in patients who complain of unsteadiness without any other symptoms and without a medical history suggestive of vestibular disorders.

Conflict of interest The authors report no conflicts of interest.

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Clinical Characteristics of Patients With Abnormal Ocular/Cervical Vestibular Evoked Myogenic Potentials in the Presence of Normal Caloric Responses

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Abstract

Objective: To investigate the clinical features and vestibular symptoms of patients with abnormal ocular vestibular evoked myogenic potentials (oVEMPs) and/or cervical VEMPs (cVEMPs) in the presence of normal caloric responses.
Study Design: Retrospective chart review.
Setting: Tertiary referral center.
Methods: One thousand five hundred twenty-one consecutive patients with balance problems who underwent the caloric, cVEMP, and oVEMP tests were included, and patients who showed abnormal oVEMPs and/or cVEMPs in the presence of normal caloric responses were selected. Clinical characteristics, diagnoses, and vestibular symptoms of the patients were analyzed.
Results: Of the 1521 patients, 227 (15%) were found to have abnormal oVEMPs and/or cVEMP responses with normal caloric responses. Benign paroxysmal positional vertigo (BBPV), Meniere's disease, and vestibular migraine were the common diagnoses of these patients. Eighty-one patients (36%) could not be diagnosed with a recognizable disease. Multiple episodes of spinning vertigo with a duration of seconds to hours were their most common vestibular symptoms.
Conclusion: BPPV, Meniere's disease, and vestibular migraine are the most frequent diagnoses showing abnormal oVEMP and/or cVEMPs without canal paresis. Apart from these clinical entities, a portion of undiagnosed patients with multiple episodes of vertigo might have a disease that involves the otolith organs only.

Keywords

vestibular, otolith, vestibular evoked myogenic potential, saccule, utricle

Introduction

The vestibular labyrinth, which is composed of 2 otolith organs and 3 semicircular canals, provides a sense of balance and orientation. Dysfunction of the vestibular labyrinth causes various kinds of vertigo and/or dizziness depending on the time-course of the disease and the extent of the lesion in the inner ear.[1] Lateral semicircular canal function in patients with vertigo or dizziness has been widely evaluated with caloric testing,[1,2] and hence it is well known that rotatory vertigo is the most common symptom of patients with acute dysfunction of their semicircular canals. On the other hand, less is known about the vestibular symptoms caused by dysfunction of the otolith organs since evaluation of the function of otolith organs has previously been difficult.

Vestibular evoked myogenic potentials (VEMPs) recorded by surface electrodes have been used clinically to assess vestibular function.[3-5] Cervical vestibular evoked myogenic potentials (cVEMPs) that are recorded from the sternocleidomastoid muscles (SCMs) in response to air-conducted stimulations (ACS) have been used to evaluate the function of the saccule and its afferents.[3,5] Recent investigations have revealed that VEMPs can also be recorded from muscles beneath the eyes in response to ACS and bone-conducted vibration (BCV).[6] These potentials are called ocular vestibular evoked myogenic potentials (oVEMPs) and are considered to represent the function of

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the utricle and its afferents mediated by a crossed otolith-ocular pathway.[7-10] Combined use of cVEMPs, oVEMPs, and caloric testing has enabled us to examine the function of the saccule, utricle, and lateral semicircular canals separately.

Previous studies have reported that patients who have characteristic vestibular symptoms, such as drop attacks, tilting, or translational sensation, tend to show abnormal cVEMP and/or oVEMP responses.[11-15] However, it is still unclear whether dysfunction of the otolithic organs causes other types of dizziness. We previously studied the clinical features of diseases showing abnormal cVEMPs to ACS in the presence of normal caloric responses[16] and reported that some patients who were diagnosed as having a disease involving the saccule and its afferents showed various types of vertigo or dizziness, including rotatory vertigo, tilting sensation, and disequilibrium. In the present study, we examine the clinical features and vestibular symptoms of patients who show abnormal oVEMP and/or cVEMP responses in the presence of normal caloric responses.

Materials and Methods

Patients

This retrospective data collection study was approved by the regional ethical standards committee in the Faculty of Medicine at the University of Tokyo (No. 2487) and conducted according to the tenets of the Declaration of Helsinki.

We reviewed the clinical records of 1521 consecutive patients with dizziness who underwent caloric, cVEMP, and oVEMP testing at the Balance Disorder Clinic at the University of Tokyo Hospital between January 2009 and December 2013. All of these patients had received a detailed history taking and a battery of tests including a physical examination and standardized neurological, neurotological, and audiological examinations. The neurotological examination included testing for spontaneous nystagmus with and without Frenzel goggles, nystagmus evoked by head shaking, positional nystagmus in the supine and head-hanging positions, as well as gaze-evoked nystagmus in the horizontal and vertical plane. Smooth pursuit and saccades were also tested, as well as the vestibulo-ocular reflex (VOR) in response to a head impulse test in the horizontal plane. Balance tests included the Romberg test and walking in a straight line. Neuroimaging studies such as computed tomography and magnetic resonance imaging of the brain were performed in 54% of the patients.

Clinical diagnoses of benign paroxysmal postural vertigo (BPPV),[17] Meniere's disease,[18] vestibular migraine,[19] psychiatric dizziness,[20] and inferior vestibular neuritis[21] were made according to published criteria for those conditions. Classification of vestibular symptoms were made according to the Barany Society's International Classification of Vestibular Disorders (ICVD).[22] In this ICVD, vertigo is defined as a false or distorted sense of rotation, translation, or tilt of self-environment; dizziness is defined as a non-vertiginous sense of disturbed or impaired spatial orientation; and unsteadiness as a feeling of swaying, rocking, instability while sitting, standing, or walking.

Vestibular Function Tests

oVEMPs to ACS and BCV. The methods for recording oVEMPs to ACS and BCV have been described in detail elsewhere.[7,10,23] In brief, with the subject in a supine position, EMG electrodes were placed on the skin 1 cm below (active) and 3 cm below (indifferent) the center of each lower eyelid. The ground electrode was placed on the chin. During testing, the subject looked up approximately 30° above straight ahead and maintained their focus on a small dot approximately 1 m from their eyes. The signals were amplified by a differential amplifier (bandwidth: 0.5-500 Hz), and the unrectified signals were averaged (n = 50) using Neuropack Σ (Nihon Kohden, Tokyo, Japan).

The ACS stimuli were short tone bursts of 4 ms duration at 500 Hz (rise/fall time = 1 ms and plateau time = 2 ms) presented separately to each ear through calibrated headphones (type DR-531, Elega Acoustics Co, Ltd, Tokyo, Japan). The stimulus intensity was set at 135 dB SPL. The stimuli were delivered 5 times per second. When using ACS, the n10 responses were measured beneath the eye contralateral to the stimulated ear;[7] the amplitude of these contralateral responses was used for calculation of the asymmetry ratio when using ACS. The BCV stimuli were 4 ms tone-bursts of 500 Hz vibration delivered by a handheld 4810 mini-shaker (Bruel and Kjaer, Naerum, Denmark) fitted with a short rod terminated in a bakelite cap 1.5 cm in diameter, which was placed, without pressure, perpendicularly on the forehead at the hairline in the midline (Fz). The driving voltage was 80 V peak to peak, and it produced a peak force level of 128 dB re 1 μN. This BCV caused a linear acceleration in the inter-aural axis at the mastoids with a maximal acceleration of approximately 0.4 g peak to peak as measured by linear accelerometers placed on the skin over the mastoid. The stimuli were applied 3 times per second, and the time window for analysis was 50 ms. Two sets of 50 stimuli were averaged.

We analyzed the amplitude of the first negative peak (n10). The latency was measured from the onset of the stimulus to the peak. The amplitude was measured from the baseline to the peak. We calculated the asymmetry ratio (AR) for n10 amplitude (oVEMP AR) with the following formula using the n10 amplitude beneath the eye ipsilateral to the affected side (Aa) and beneath the eye ipsilateral to the un affected side (Au):

$$\text{oVEMP AR } (\%) = 100 * \left((\text{Aa} - \text{Au}) / (\text{Aa} + \text{Au}) \right).$$

The upper limit for the normal oVEMP AR was set at 27.3 for oVEMPs to BCV[23] and at 34.4 for oVEMPs to ACS.[7] When no reproducible n10 was present in 2 runs, we classified the response as being "absent." When a reproducible n10 was present and the AR was greater than the normal upper limits, we classified the response as "decreased." We regarded both "absent" and "decreased" responses as abnormal responses for the purpose of our analyses. With regard to oVEMPs to ACS, we judged only the patients with unilaterally abnormal responses as abnormal, excluding the patients with bilaterally absent responses from the abnormal group, since oVEMPs to ACS are reported to be absent in approximately 10% of normal healthy subjects.[24]

cVEMPs to ACS. To record cVEMPs, the EMG electrodes were placed at symmetrical sites over the upper half of the sternocleidomastoid muscles, with reference electrodes on the side of the upper sternum. The ground electrode was placed on the nasion. The signals from the stimulated side were amplified by a differential amplifier (20-2000 Hz), and the unrectified signals were averaged (n = 100). Short tone bursts (500 Hz, 4 ms, 135 dBSPL) were delivered through headphones. The patients were instructed to contract their SCM during testing by lifting their head off the pillow. During the recording, EMG activity of the SCMs was monitored on a display to ensure that muscle activity was maintained at a sufficient level (>150 μV) in each patient. We analyzed the first biphasic responses (p13-n23) from the ipsilateral SCM to the stimulated side. We calculated the asymmetry ratio for the amplitude of cVEMPs (cVEMP AR) with the following formula using the amplitude of p13-n23 on the affected side (Aa) and that on the unaffected side (Au):

$$\text{cVEMP AR }(\%) = 100 * \left(\left(Au - Aa\right)/\left(Au + Aa\right)\right).$$

On the basis of results from normal subjects, the upper limit for the cVEMP AR was set to 34.0.[25] When no reproducible p13-n23 was present in 2 runs, we regarded it as an "absent" response. When a reproducible p13-n23 was present and the AR was greater than the predefined upper limit for normal subjects, we regarded it as a "decreased" response. Both "decreased" and "absent" responses were classified as abnormal responses.

Caloric tests. Caloric testing was performed by irrigating the external auditory canal with 2 ml ice water (4°C) for 20 seconds followed by aspiration of water. This method of caloric stimulation is easier to perform than bithermal irrigation with water at 30° and 44° C and has been shown to have a high sensitivity and specificity for detecting canal paresis (CP) based on Jongkee's formula.[26] Caloric nystagmus was recorded, in a darkened room, using an electronystagmograph. We defined an abnormal caloric response by either of the following criteria: (1) CP percentage >20%[16] and (2) maximum slow phase eye velocity <10°/s bilaterally.[27]

Classification of patients. We classified patients based on the results of oVEMPs and cVEMPs. Patients who showed abnormal oVEMP responses with normal cVEMP responses were classified as oVEMP–/ cVEMP+, those who showed normal oVEMP responses with abnormal cVEMP responses as oVEMP+/ cVEMP–, and those who showed abnormal oVEMP responses as well as abnormal cVEMP responses as oVEMP–/ cVEMP–.

Statistical analysis. A comparison of the age and sex in each group was made using the Kruskal-Wallis test (P < .05); the Steel-Dwass multiple comparison test was performed to compare all pairs of means (P < .05). IBM SPSS statistics 21 (IBM Corporation, New York City, New York, USA) was used for the statistical analysis.

Case Report

A 51-year-old man suddenly felt a to-and-fro sensation with nausea lasting 5 minutes while sitting on a chair in his office. He had no associated complaints of hearing loss, tinnitus, fullness in the ears, headache, or changes in his strength or sensation. After this episode, he had similar episodes a few times per week. He had no previous history of vestibular symptoms. There was no significant past medical history. The family history was not contributory.

On examination at 1 month after the onset of symptoms, he underwent audio-vestibular testing. He had a spontaneous, right-beating nystagmus under Frenzel goggles, but it disappeared without the goggles. Turning the head to the left in the supine position increased the slow-phase eye velocity of the spontaneous nystagmus, but this patient did not have BPPV. The Romberg test and Fukuda (Unterberger) test both gave negative results. A pure-tone audiogram revealed normal hearing in both ears. The head impulse test and caloric test showed normal semicircular canal function in the horizontal plane. In oVEMPs to BCV, the n10 response recorded from the right eye was absent, while the response from the left eye showed normal n10 responses (Figure 1). cVEMPs to air-conducted sound were normal on both sides. Magnetic resonance imaging of the brain showed normal findings.

The patient was diagnosed as having otolithic dysfunction and was classified as oVEMP–/cVEMP+.

Results

Of the 1521 patients who underwent oVEMP, cVEMP, and caloric testing, 227 patients (15%; 91 men and 136 women; mean age ± SD: 51.4 ± 17.5 years) were found to show

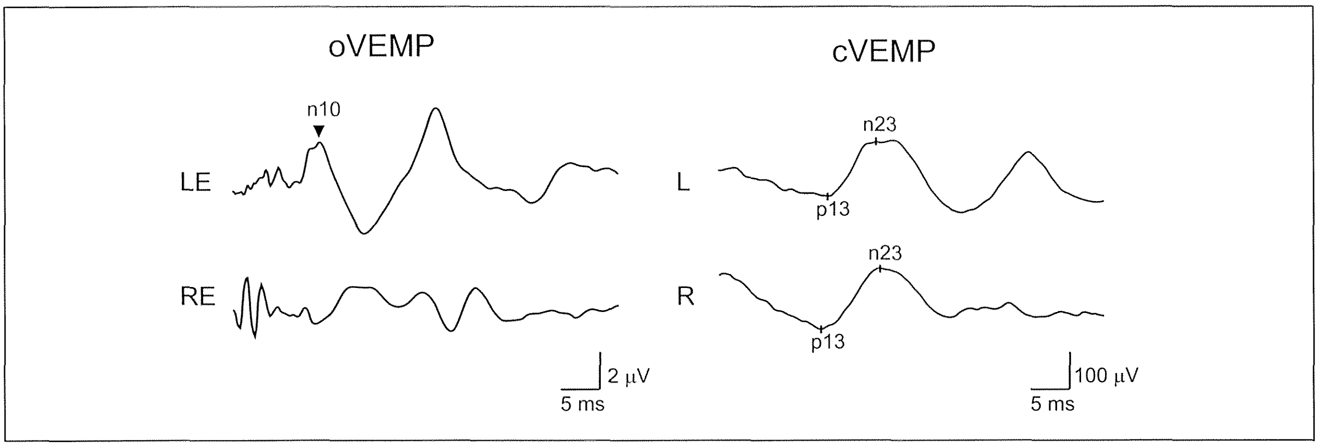

Figure 1. oVEMP and cVEMP in a patient (51-year-old) classified into the oVEMP–/cVEMP+ group. In oVEMPs to bone-conducted vibration (left panel), the n10 response recorded from the right eye was absent, while the response from the left eye showed normal n10 responses. cVEMPs to air-conducted sound were normal on both sides. Magnetic resonance imaging of the brain showed normal findings.

Abbreviations: cVEMPs, cervical vestibular evoked myogenic potentials; L, left side; LE, left eye; oVEMPs, ocular vestibular evoked myogenic potentials; R, right side; RE, right eye.

Table 1. Clinical Diagnoses of Patients With Abnormal oVEMPs and/or cVEMPs Without Canal Paresis.

Diagnosis	oVEMP–/cVEMP+ (%)	oVEMP+/cVEMP– (%)	oVEMP–/cVEMP– (%)
BPPV	6 (11.3)	9 (8.8)	6 (8.3)
Vestibular migraine	6 (11.3)	9 (8.8)	6 (8.3)
Psychiatric dizziness	5 (9.4)	8 (7.8)	5 (6.9)
Meniere's disease	4 (7.5)	12 (11.8)	11 (15.3)
Acoustic neuroma	3 (5.7)	2 (2)	5 (6.9)
Inferior VN	0 (0)	4 (3.9)	2 (2.8)
Others	12 (33.3)	16 (15.7)	15 (20.8)
Undetermined	17 (32.1)	42 (41.2)	22 (30.6)
Total	53 (100)	102 (100)	72 (100)

Abbreviations: BPPV, benign paroxysmal positional vertigo; cVEMPs, cervical vestibular evoked myogenic potentials; oVEMPs, ocular vestibular evoked myogenic potentials; VN, vestibular neuritis.

abnormal oVEMP and/or cVEMP responses with normal caloric responses. All of these patients showed normal responses in horizontal head impulse test bilaterally. Among them, 53 patients (23%; 20 men and 33 women; 51.3 ± 18.3 years) showed abnormal oVEMP responses with normal cVEMP responses (oVEMP–/cVEMP+), 102 patients (45%; 43 men and 59 women; 50.2 ± 17.7 years) showed normal oVEMP responses with abnormal cVEMP responses (oVEMP+/cVEMP–), and the remaining 72 patients (32%; 44 men and 28 women; 53.4 ± 16.5 years) showed abnormal oVEMP responses as well as abnormal cVEMP responses (oVEMP–/cVEMP–). The majority of the oVEMP–/cVEMP– group were male, while the majority were female in the other 2 groups. There was a significant difference in the sex ratio among the 3 groups ($P < .05$). There was no significant difference in the mean ages among the 3 groups ($P > .7$).

Table 1 shows the clinical diagnoses of patients who showed abnormal oVEMPs and/or cVEMPs without canal paresis. BPPV and vestibular migraine were the most common diagnoses in the oVEMP–/cVEMP+ group, whereas Meniere's disease was the most common in both the oVEMP+/cVEMP– and the oVEMP–/cVEMP– groups. BPPV, vestibular migraine, psychiatric dizziness, and Meniere's disease comprised approximately 40% of the diagnoses in each group. Other diagnoses included vestibular schwannoma, orthostatic hypotension, and vertebrobasilar insufficiency. Eighty-one (36%) of the patients who showed abnormal oVEMPs and/or cVEMPs without canal paresis did not have a recognized disease entity.

Table 2 shows the clinical characteristics of patients without diagnoses who had abnormal oVEMPs and/or cVEMPs without canal paresis. The mean ages of all 3 groups were in the mid 50s. Male patients were

Table 2. Clinical Characteristics of Undiagnosed Patients With Abnormal oVEMPs and/or cVEMPs Without Canal Paresis.

	oVEMP–/cVEMP+ (n = 17)	oVEMP+/cVEMP– (n = 42)	oVEMP–/cVEMP– (n = 22)
Male/female	10/7	19/23	10/12
Age	56.7 ± 16.4	56.5 ± 14.7	53.9 ± 16.9
Abnormal cVEMP			
Unilateral	0	41 (98)	14 (64)
Bilateral	0	1 (2)	8 (36)
Abnormal oVEMP			
Unilateral	16 (94)	0	21 (95)
Bilateral	1 (6)	0	1 (5)
Nystagmus	4 (24)	9 (21)	5 (23)
Horizontal	4	9	5
Downbeat	0	1	0
Upbeat	0	0	1

Abbreviations: cVEMPs, cervical vestibular evoked myogenic potentials; oVEMPs, ocular vestibular evoked myogenic potentials.

Table 3. Vestibular Symptoms in Patients With Abnormal oVEMPs and/or cVEMPs Without Canal Paresis.

Vestibular Symptoms	oVEMP–/cVEMP+ (%)	oVEMP+/cVEMP– (%)	oVEMP–/cVEMP– (%)
No. of episodes			
Single	3 (18)	4 (10)	3 (24)
Multiple	13 (76)	36 (86)	18 (82)
Chronic	1 (6)	2 (5)	1 (5)
Vertigo			
Spontaneous, spinning vertigo	4 (23.5)	21 (50)	11 (50)
Spontaneous, non-spinning vertigo	2 (11.8)		1 (4.5)
Visually induced, non-spinning vertigo	1 (5.9)		
Valsalva-induced, non-spinning vertigo	1 (5.9)		
Dizziness			
Spontaneous dizziness	6 (35.3)	8 (19)	
Positional dizziness	3 (17.6)	7 (16.7)	4 (18.2)
Orthostatic dizziness		1 (2.4)	4 (18.2)
Unsteadiness		3 (7.1)	2 (9.1)
Visual tilt		1 (2.4)	
Directional pulsion		1 (2.4)	
Total	17 (100)	42 (100)	22 (100)

Abbreviations: cVEMPs, cervical vestibular evoked myogenic potentials; oVEMPs, ocular vestibular evoked myogenic potentials.

predominant in the oVEMP–/cVEMP+ group (59%), whereas female patients were predominant in the oVEMP+/cVEMP– group (55%) and oVEMP–/cVEMP– group (55%). Spontaneous nystagmus was observed under Frenzel goggles in approximately 20% of the patients in each group, most of which was horizontal. One patient in the oVEMP+/cVEMP– group and 1 patient in the oVEMP–/cVEMP– group had downbeat and upbeat components of nystagmus, respectively, which were mixed with horizontal components.

Table 3 shows the vestibular symptoms in undiagnosed (undetermined) patients with abnormal oVEMPs and/or cVEMPs without canal paresis. The majority of patients in each group had experienced multiple episodes of vestibular symptoms. Vertigo had been experienced by approximately 50% of the patients in each group. In the oVEMP–/cVEMP+ group, a half of the patients had spinning vertigo with a duration of minutes to hours while the others showed non-spinning vertigo, most of which lasted less than 1 minute. In the oVEMP+/cVEMP– and oVEMP–/cVEMP– groups, most patients experienced the spinning form of vertigo. Symptoms of non-spinning vertigo included swaying (n = 2) and tilting (n = 1) sensations. Approximately half of the patients in each group had dizziness or unsteadiness. Among these patients, spontaneous dizziness was most frequent in the oVEMP+/cVEMP– and oVEMP–/cVEMP+ groups, whereas positional or orthostatic dizziness were most frequent in the oVEMP–/cVEMP– group. A drop attack, which is classified as directional pulsion, was observed in only 1 patient in the oVEMP+/cVEMP– group.

Discussion

The use of oVEMPs as well as cVEMPs has enabled clinicians to explore vestibular abnormalities in more detail.[4,5] Clinical and neurophysiological studies have suggested that cVEMPs in response to ACS reflect function in the saccule and inferior vestibular nerve,[5] whereas oVEMPs to ACS as well as BCV primarily reflect function in the utricle and superior vestibular nerve.[8,9] Combined use of cVEMPs, oVEMPs, and caloric testing has enabled us to examine the function of the saccule, utricle, and the lateral semicircular canals separately. To clarify the clinical features of dizziness caused by the otolithic organs, we retrospectively studied the clinical characteristics of patients with dizziness who showed abnormal oVEMP and/or cVEMP responses with normal caloric responses.

In the present study, approximately 15% of patients with dizziness showed abnormal oVEMP and/or cVEMP responses with normal caloric responses. Among them, the oVEMP+/cVEMP– group was the most frequent (45%), followed by the oVEMP–/cVEMP– group (32%) and oVEMP–/cVEMP+ (23%) group. The clinical diagnoses of the patients were different among these 3 groups: BPPV and vestibular migraine were most frequent in the oVEMP–/cVEMP+ group, while Meniere's disease was most frequent in both the oVEMP+/cVEMP– and oVEMP–/cVEMP– groups. BPPV has been considered to be caused by canalolithiasis and cupulolithiasis in the semicircular canals.[28] In addition to these mechanisms, utricular dysfunction has also been suggested as a possible mechanism of BPPV.[29] Nakahara et al[29] reported that patients with BPPV have a tendency to show abnormal oVEMPs more frequently than cVEMPs, consistent with our study. Vestibular migraine is increasingly recognized as a frequent cause of vestibular symptoms.[19] Its pathophysiology is still unclear, and there is ongoing debate as to whether its origin is central or peripheral.[30] It has been reported that patients with vestibular migraine show abnormal oVEMPs as well as cVEMPs more frequently than normal subjects, suggesting that at least a portion of patients with vestibular migraine have dysfunction of the otolithic organs or their afferents.[31,32] Abnormal cVEMPs as well as oVEMPs in Meniere's disease have been reported by several groups, and approximately half of Meniere's disease patients show abnormal cVEMPs and/or oVEMPs during the quiescent period.[33,34] A human temporal bone study showed that endolymphatic hydrops was most frequently observed in the saccule, followed by the cochlear, utricle, and the semicircular canals.[35] Young et al[34] advocated the use of oVEMP, cVEMP, and caloric tests to assess the extent of endolymphatic hydrops in the inner ear in Meniere's disease.

In the current study, 36% (81/225) of the patients who showed abnormal oVEMPs and/or cVEMPs with normal caloric responses could not be diagnosed with an established clinical entity. Most of these patients showed normal results on audiologic and neurotologic tests, except for VEMP responses. Since oVEMP as well as cVEMP responses are considered to be clinical tests of the otolith organs, dysfunction of the otolith organs sparing the semicircular canals were considered to be present in these patients. Such patients would be expected to have vertical or vertical/torsional nystagmus during attacks since electrical stimulation of the saccule or the utricle produces vertical or vertical torsional nystagmus in mammals.[36-38] However, in the present study, only approximately 20% of these patients showed spontaneous nystagmus during testing, and this was mostly horizontal. Recently, Manzari et al[39] reported an unsteady patient with horizontal nystagmus who showed normal head impulse tests but abnormal oVEMPs to BCV unilaterally. They speculated that spontaneous horizontal nystagmus could be caused by dysfunction of the utricle, since otolithic stimulation generated by linear acceleration modulates the slow-phase eye velocity of horizontal nystagmus via the widespread convergence of neural inputs from the otoliths onto horizontal canal neurons in the vestibular nuclei.[40]

Vestibular symptoms caused by otolithic dysfunction have traditionally been suggested as a tilting sensation, a sense of moving to and fro, lateropulsion, or feelings of falling, based on physiological evidence that the otolithic signals play an important role in the sense of uprightness and postural control and in the perception of linear motion.[41] Recent studies have shown that patients who complained of a forward or backward pulling sensation, episodic tilt, or a translational sensation have a tendency to show abnormal oVEMP and/or cVEMPs, suggesting these symptoms are caused by dysfunction of the otolith organs.[11-15] In the present study, spinning vertigo was the most frequent vestibular symptom in undiagnosed patients showing abnormal oVEMP and/or cVEMPs without canal paresis. Although the direction of the spinning vertigo was not known in most patients, they might include vertigo in the yaw, roll, or pitch planes since stimulation of the saccule or utricle can produce horizontal,[40] vertical, or vertical-torsional nystagmus.[36] Non-spinning vertigo, such as swaying and tilting, was more frequently observed in the oVEMP–/cVEMP+ group than in the other 2 groups, suggesting an association of the symptoms with utricular dysfunction.[12,13] Spontaneous and positional dizziness were also common in all the 3 groups, and these symptoms have been regarded as indicative of otolith dysfunction.[29,41] Although Tumarkin's drop attacks have been implicated as a representative symptom of utricular dysfunction,[42] there was only 1 patient in the oVEMP+/cVEMP– group who experienced these attacks. Patients with Meniere's disease who had experienced drop attacks were reported to show abnormal oVEMPs as well as cVEMPs more frequently than those who had not expereinced drop attacks.[43]

The etiologies of otolith dysfunction are unknown and may be heterogeneous. Since most patients had multiple episodes of vertigo or dizziness with the duration from seconds to hours, they might have a distinct pathology other than vestibular neuritis, such as endolymphatic hydrops, ischemia, or an autoimmune condition. Calzada et al[44] examined the otolithic membrane of patients who had had multiple episodes of Tumarkin's drop attacks without Meniere's disease and reported that they had damaged otolithic membranes in the utricle. They speculated that the underlying pathology in drop attacks results from injury to the otolithic membrane, resulting in free-floating otoliths and atrophy, although it remains unclear how the damaged otolithic membranes cause multiple vestibular drop attacks.

Our study has some limitations. First of all, this is a retrospective study. There might be some bias in the distribution of the patients who showed abnormal oVEMP and/or cVEMP responses with normal caloric responses. Second, there are differences in the sensitivity and the specificity among oVEMPs, cVEMPs, and caloric tests. They might affect the classification of the patients. Third, the responses of the anterior or posterior canals were not measured. To measure function of these canals, a quantitative head impulse test is required. Fourth, vestibular functions was measured in the quiescent period. It is possible that vestibular symptoms were caused by semicircular canals dysfunction, which had returned to normal before the vestibular testing was performed.

In conclusion, we sought patients who had vestibular symptoms and showed abnormal oVEMP and/or cVEMPs without canal paresis. Among these patients, BPPV, vestibular migraine, Meniere's disease, and psychiatric dizziness were the most frequent diagnoses. At least a portion of the undiagnosed patients might have had vestibular symptoms caused only by dysfunction of the otolith organs. Their symptoms were various, but the most frequent vestibular symptoms were multiple episodes of spinning vertigo with a duration of seconds to hours. The underlying pathologies are still unknown. To clarify these, a more elaborate estimation of the function of the otolith organs and semicircular canals and accumulation of pathological evidence are required.

Declaration of Conflicting Interests

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Short communication

The effect of aging on the center-of-pressure power spectrum in foam posturography

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HIGHLIGHTS

- We assess aging effect on center-of-pressure power spectrum in foam posturography.
- Especially, the eyes open/foam rubber condition highlights age-related changes.
- Age-related changes were found in not only older but early-middle-aged subjects.

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ABSTRACT

To assess age-related frequency-domain characteristics of the sway of center of pressure (COP) in foam posturography, two-legged stance tasks were performed by 163 controls in 4 conditions: eyes open with and without foam rubber, and eyes closed with and without foam rubber. The areas under the curve (AUCs) of power spectral density of the COP were calculated across low frequency (≥0.02 Hz and <0.1 Hz, LF-AUC), middle frequency (≥0.1 Hz and <1 Hz, MF-AUC) and high frequency (≥1 Hz and <10 Hz, HF-AUC) ranges. We categorized the controls into 7 age groups and analyzed each AUC in the 4 conditions. MF- and HF-AUCs tended to show a difference between younger and older age-groups in all 4 conditions. Comparing the number of pairs in which a significant difference was shown, the condition with foam rubber, especially with eyes open, tended to highlight age-related changes. In the medial-lateral axis in the eyes open/foam rubber condition, the MF-AUC of the ≥ 75 years group was significantly larger than that of the 65–74 years group, and the MF-AUC of the 65–74 years group was significantly higher than that of the 55–64 years group, although there were no significant differences of MF-AUC among age groups under 54 years. In this condition, although HF-AUC did not change in groups over 35 years old, HF-AUC of each age group over 35 years old was significantly larger than that of the group under 24 years old. This result suggests that, in the medial-lateral axis in the eyes open/foam rubber condition, MF-AUC is specifically affected by age in late-middle-aged (ages 55–64) and older subjects, while HF-AUC is specifically affected by age in early-middle-aged (ages 35–44) subjects.

1. Introduction

Static postural control is maintained by the integration of somatosensory, visual, and vestibular components in the central nervous system, with outputs to the musculoskeletal system [14]. As age advances, the function of all components of the postural control system declines [11]. This loss of postural control in the elderly can be a significant cause of falls [16]. Identifying age-related changes in postural control is important due to the major effect of postural instability and falls on health in the elderly.

Posturography is used to evaluate static postural control. It measures the position of the center of pressure (COP) that is defined as the point on the force plate surface through which the subject's center of gravity passes. For the purpose of scrutinizing the role of different sensory inputs on static postural control, dynamic posturography using a moving platform or a foam rubber surface has been devised to allow selective manipulation of vision and somatosensation [6,18]. Our group recently reported the usefulness of posturography using a foam rubber surface, i.e., foam posturography, for assessing peripheral vestibulopathy, both in the acute and

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the chronic stages [6–9]. This system is able to detect dysfunction in both the superior and inferior vestibular nerve systems [8].

The incidence of falls increases with age, and falls in the elderly have been linked not only to intrinsic but also to extrinsic risk factors [1]. Elderly subjects have more difficulty controlling posture than young subjects when visual and proprioceptive inputs are disturbed [6,13,21]. Foam posturography has great potential as a tool to detect age-related postural change, since it can manipulate both visual and somatosensory inputs and mimic more severe extrinsic circumstances for static postural control.

For the purpose of investigating postural control in greater depth, power spectral analysis of COP sway has been performed [4,19]. The analysis is a useful technique for quantifying overall variability of COP sway as well as specific components associated with pathological and/or physiological effects that cause balance disorders. It has previously been shown that elderly subjects exhibit a shift in the distribution of spectral power from higher to lower frequencies in medial-lateral (ML) postural forces [15]. Power spectral analyses of COP sway in foam posturography might have the potential to identify a frequency domain that is sensitive to age-related changes and provide an initial step towards fall prevention and the development of medical interventions for postural decline in the elderly.

The purpose of this study is to investigate aging effects revealed by power spectral analysis of COP sway in foam posturography. We divided subjects by age in ten-year increments and investigated the difference in frequency-domain characteristics not only between younger and older age groups but also between relatively close age groups.

2. Material and methods

We enrolled 163 healthy control subjects (84 men, 79 women) in the present study. All subjects were free from episodic vertigo/

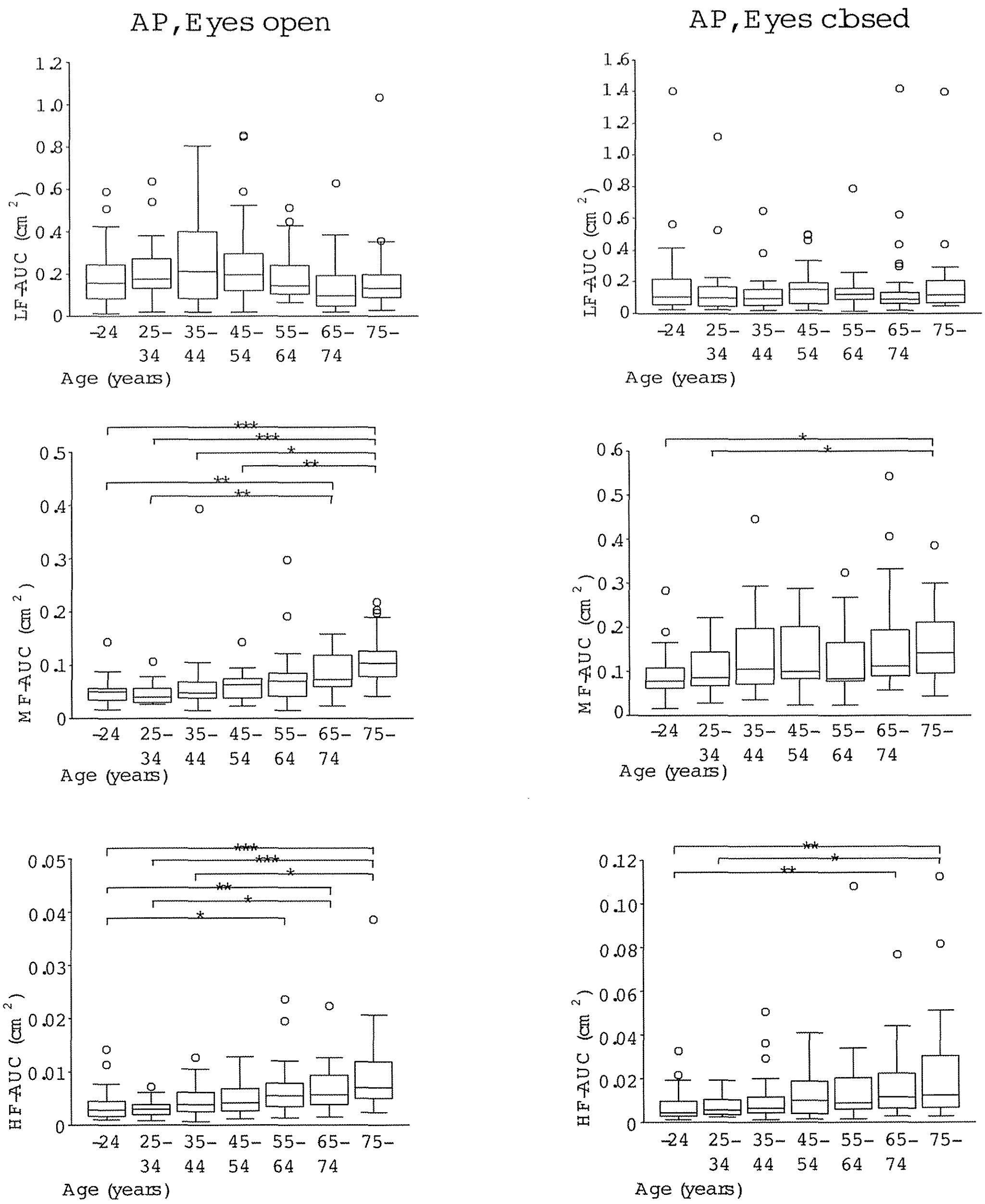

Fig. 1. Box plots of LF-, MF-, and HF-AUC of the AP axis in the condition without foam rubber in each age group. * = Significant difference in nonparametric Steel–Dwass method (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

dizziness or any obvious neurological or orthopedic disorders, and had no medical history of a psychogenic disorder, head injury, exposure to ototoxic drugs, diabetes mellitus, hypertension or coronary artery disease. These subjects were the same as our previous report [5]. The mean age (±standard deviation), height and weight of the 163 healthy control subjects were 48.7 (±22.5) years, 160.6 (±11.9) cm and 59.4 (±11.7) kg, respectively. The study was approved by the regional ethical standards committee in the Faculty of Medicine at the University of Tokyo and the Kanazawa University Department of Education. The study was conducted according to the tenets of the Declaration of Helsinki, and informed consent was obtained from each participant.

The detailed methods of foam posturography have been described previously [5,6]. Briefly, two-legged stance tasks were performed under 4 conditions: eyes open or eyes closed, with or without the foam rubber. The recording time was 60 s or until the subject required assistance to prevent falling. We estimated the power spectrum of the acceleration signal for the anterior-posterior (AP) and the medial-lateral (ML) axis by using the maximum entropy method, as we have previously reported [5]. Briefly, the area under the curves (AUCs) of power spectral density (PSD) of the COP were calculated for each axis across three frequency ranges: ≥0.02 Hz and <0.1 Hz (low-frequency range, LF-AUC), ≥0.1 Hz and <1 Hz (middle-frequency range, MF-AUC) and ≥1 Hz and <10 Hz (high-frequency range, HF-AUC).

We categorized the healthy controls into 7 groups (≤24 years, 25–34, 35–44, 45–54, 55–64, 65–74, and ≥75 years) and the non-parametric Steel–Dwass method was performed for the AUC of each frequency range of each axis in the above-mentioned 4 conditions in order to calculate statistical significances in pairs of multiple-comparisons [2,20]. A significant positive relationship was defined as having a p-value less than 0.05 in the present study.

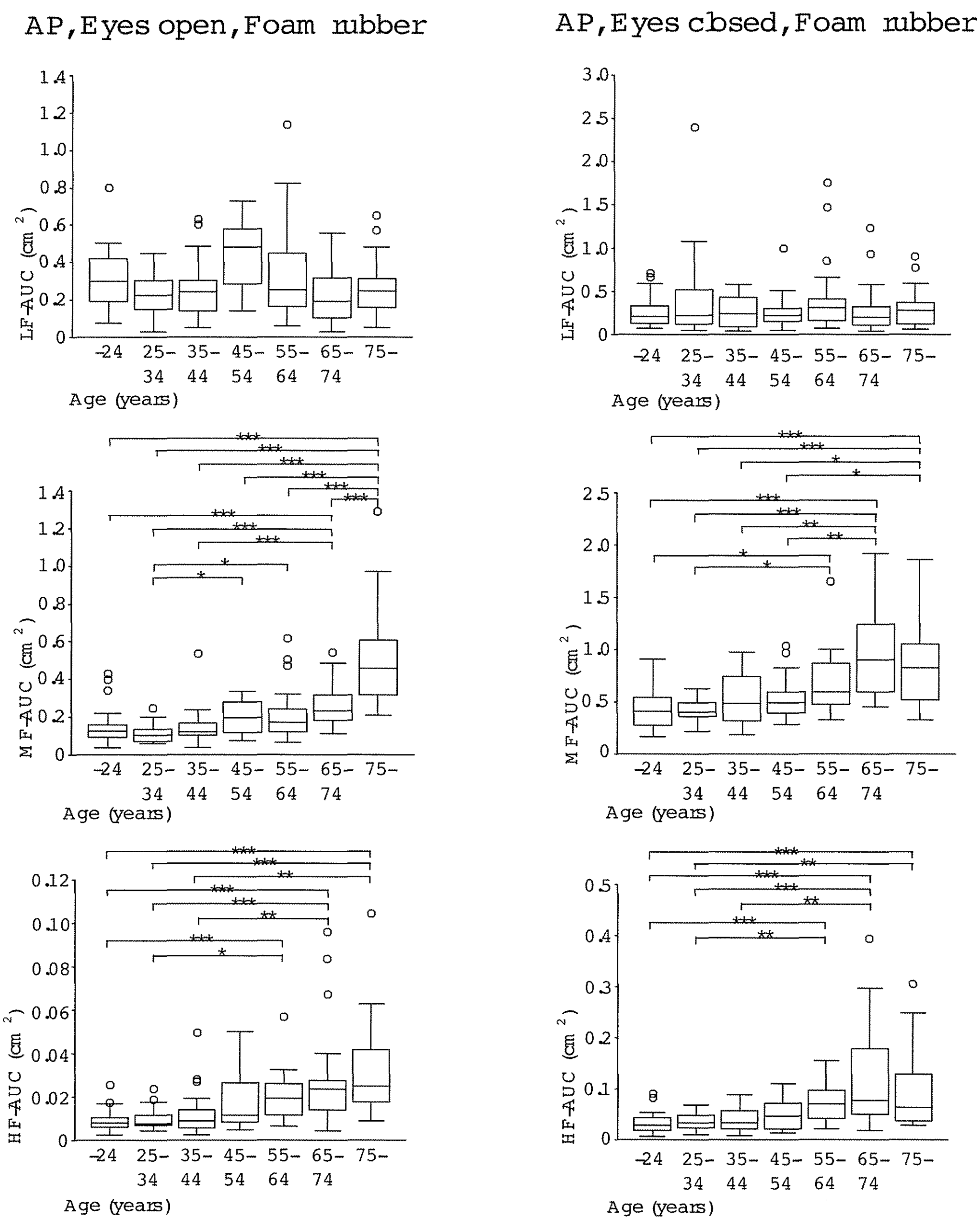

Fig. 2. Box plots of LF-, MF-, and HF-AUC of the AP axis in the condition with foam rubber in each age group. * = Significant difference in nonparametric Steel–Dwass method (*p < 0.05, **p < 0.01, ***p < 0.001).