

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.

Keywords Posture · Vestibule · Vestibular disease

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

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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 (\pm SD) age 56.5 (\pm 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 $>150 \mu\text{V}$) 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 $100[(\text{Au} - \text{Aa})/(\text{Aa} + \text{Au})]$, 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 (\pm SD) age, 60.5 (\pm 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 (\pm SD) age, 56.2 (\pm 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 (\pm SD) age, 65.8 (\pm 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

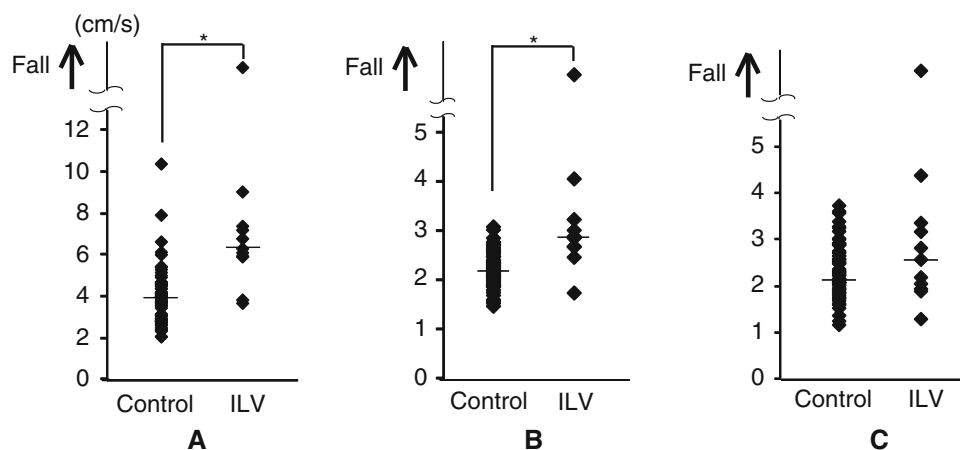


Fig. 1 Dot plots of parameters associated with the velocity in control subjects and patients with ILV. **a** Velocity with eyes closed/foam rubber. **b** Romberg's ratio of the velocity with the foam rubber. **c** Foam ratio of the velocity with the eyes closed. The dots above the undulating lines represent 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)		<i>p</i> value
			Control (<i>n</i> = 66)	ILV (<i>n</i> = 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

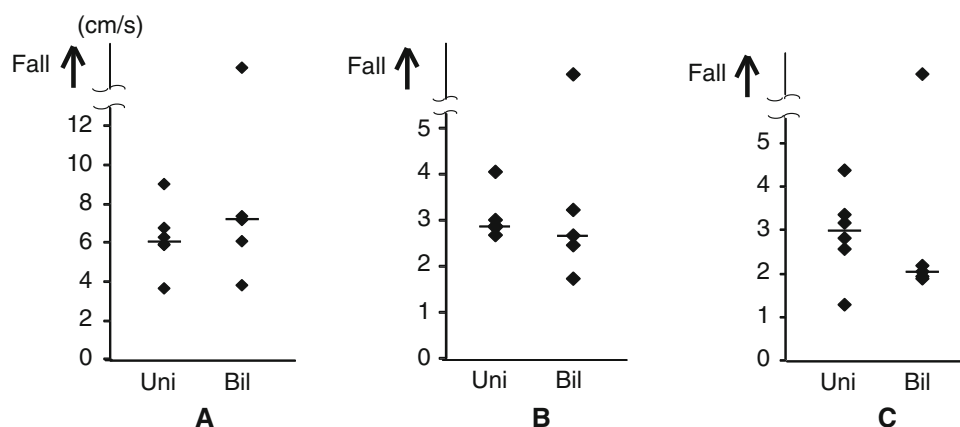


Fig. 2 Dot plots of parameters associated with the velocity in patients with unilateral and bilateral ILV. **a** Velocity with eyes closed/foam rubber. **b** Romberg's ratio of the velocity with the foam rubber. **c** Foam ratio of the velocity with the eyes closed. The dots above the undulating lines 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)		<i>p</i> value
			Unilateral ILV (<i>n</i> = 6)	Bilateral ILV (<i>n</i> = 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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