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Proposal on the Diagnostic Criteria of Definite Isolated Otolith Dysfunction

Han Gyeol Park, Jun Ho Lee, Seung Ha Oh, Moo Kyun Park, and Myung-Whan Suh

Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul, Korea

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Address for correspondence
Myung-Whan Suh, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery,
Seoul National University Hospital,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea
Tel +82-2-2072-4845
Fax +82-2-766-2447
E-mail drmung@naver.com

Background and Objectives: Dizzy patients with abnormal otolith function tests, despite a normal caloric response, are defined as having specific (isolated) otolith organ dysfunction. This study was performed to compare the differences in clinical presentation between isolated otolith dysfunction (iOD) patients with lab- and Sx-based iOD group and lab-based iOD symptoms. **Subjects and Methods**: The medical records of 23 iOD patients with normal caloric response but abnormal cervical vestibular evoked myogenic potential (VEMP), ocular VEMP, or subjective visual vertical were reviewed. Non-spinning vertigo was considered as otolith-related symptoms. The patients' age, onset of dizziness, Numeric Rating Scale on the severity of dizziness, and concomitant vestibular disorders were analyzed. **Results**: Patients in the lab-based iOD group were significantly older than those in the lab- and Sx-based iOD group. Known vestibular disorders were significantly more common in the lab-based iOD group (83.3%) compared to the lab- and Sx-based iOD group (18.2%). Despite the normal caloric response, catch-up saccade was found in the video head impulse test in more than half (54.5%) of the lab-based iOD group patients. There was no catch-up saccade in the lab- and Sx-based iOD group. There were no significant differences in gender ratio, frequency of dizziness attacks, and duration of illness. **Conclusions**: We propose new definitions of definite iOD (lab- and Sx-based iOD) and probable iOD (lab- or Sx-based iOD). These new definitions may help researchers to identify patients who are more likely to have true iOD, and facilitate comparisons of results between different studies.**J Audiol Otol 2019;23(2):103-111**

KEY WORDS: Otology · Vestibular · Dizziness · Otolith dysfunction

Introduction

Some patients with dizziness show abnormal findings in otolith function tests despite normal semicircular canal (SCC) function [1]. The dizziness in such cases is presumed to be due to an otolith organ-specific (isolated) disorder. The saccule and utricle are sensors of linear acceleration. Therefore, isolated otolith dysfunction (iOD) [2] may produce symptoms such as tilting, translational sensations in the roll plane [2], translational sensations in the pitch plane [3], or drop attacks. It has been reported that patients with otolith function-related symptoms have a greater chance of positive findings in cervical vestibular evoked myogenic potential (cVEMP) and ocular vestibular evoked myogenic potential (oVEMP) (symptom-driven approach) [4]. It has also been reported that patients with abnormal otolith function lab findings have a greater likelihood of swaying or rocking type dizziness (lab finding-driven approach) [5]. However, there is no consensus on symptom definition and diagnostic criteria for otolith dysfunction. Furthermore, there is still a lack of consensus and standardization with regard to the test battery to be used for assessment of otolith function [6]. Therefore, it is necessary to determine a set of diagnostic criteria for iOD with a structured definition based on the symptoms and lab findings.

Several different terms have been used to indicate iOD by different researchers. For example, some authors used the term "idiopathic otolithic vertigo (IOV)" [2], defined as 1) episodic lateral tilting or translational sensations, or 2) episodic anteroposterior tilting or translational sensations, or 3) episodic up-down translational sensations. Others have intro-

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duced the term "otolith organ-specific vestibular dysfunction (OSVD)" [1], defined as abnormal cVEMP responses to air-conducted sound and/or oVEMP responses to bone-conducted vibration in the presence of normal caloric responses and normal video head impulse test (vHIT) recordings in each SCC plane. Isolated utricular dysfunction (iUD) has also been defined as the presence of a unilateral oVEMP abnormality and normal caloric responses [5]. Although the definitions are slightly different, terms such as IOV, OSVD, and iUD are all aimed at classifying a specific group of patients with abnormal otolith organ function and normal SCC function. In most of the studies mentioned above, a normal caloric response was a prerequisite to guarantee normal SCC function [1,5,7]. However, the false negative outcome of the caloric test in some patients may make this classification obscure. Some patients classified as OSVD or iUD in previous reports may not have had true iOD. It is possible that a significant proportion of patients in this group also had SCC dysfunction, but the caloric test results were normal due to false negative error. For example, the most common symptom of OSVD was rotatory vertigo [1]. As physiologically rotatory vertigo is attributable to dysfunction of the SCC, we believe that the patients in this previous study did not represent true iOD. To overcome such problems, we propose that lab findings as well as symptoms should be taken into consideration in the diagnostic criteria of iOD.

This study was performed to classify iOD patients into two groups: an iOD group proven by lab findings (caloric and otolith function tests) without iOD symptoms (lab-based iOD group) and an iOD group proven by lab findings with accompanying iOD symptoms (lab- & Sx-based iOD group). We hypothesized that the clinical presentation of these two groups would be different because of differences in the true extent of the pathology in the inner ear. Despite the normal caloric response, both the SCC and otolith organs may be compromised in the lab-based iOD group, while the SCC is preserved and only the otolith organs are compromised in the lab- & Sx-based iOD group. We believe this study will help us understand a novel disease entity that has not been fully recognized in the past and understand the underlying mechanism of dizziness in some patients who cannot be fully explained by the classical vestibular function tests (VFT) (caloric test and/or rotation chair test).

Subjects and Methods

The study was performed according to a retrospective medical chart review protocol.

Participants and groups

Data from patients who visited Seoul National University Hospital dizziness clinic between October 2013 and September 2016 were analyzed retrospectively. Twenty-three patients with iOD were enrolled in the study. The definition of iOD was 1) normal caloric response and 2) abnormal otolith function test: cVEMP, oVEMP, or subjective visual vertical (SVV). We did not include vHIT in the inclusion criteria, because 1) vHIT is a new test needing more verification in terms of iOD and 2) we wanted to compare our results with that of the former studies (performed before the vHIT era). Structured history taking and comprehensive VFT were performed for all 23 patients. According to the first International Classification of Vestibular Disorders (ICVD-I) of the Barany Society, vertigo was defined as the sensation of self-motion in the absence of self-motion or a sensation of distorted self-motion during an otherwise normal head movement [8]. Vertigo was further subdivided into spinning sensations (spinning vertigo) and other false sensations (non-spinning vertigo) according to the ICVD-I [8]. Horizontal floating sensation, flipping upside down, lateral translation, and up-down vibration were classified as non-spinning vertigo. As these four symptoms are thought to be related to inappropriate sensation of horizontal (utricle) or vertical (saccule) acceleration, they were also defined as otolith organ-related symptoms. Patients were classified into the lab- & Sx-based iOD group (iOD with otolith organ-related symptoms, n=11) and lab-based iOD group (iOD without otolith-related symptoms, n=12). The subjective sensation of dizziness was "spinning vertigo" in all patients in the lab-based iOD group. Patient's age, onset of dizziness, Numeric Rating Scale (NRS) for severity of dizziness (10, worst possible dizziness ever experienced; 0, no dizziness), concomitant vestibular disorders, and other VFT findings were analyzed.

Vestibular function test

As a diagnostic work up, videonystagmography of spontaneous and positional nystagmus, caloric test, cVEMP, oVEMP, SVV, vHIT and Modified Clinical Test of Sensory Interaction on Balance (mCTSIB) were performed. Bithermal caloric test was performed with cool (30°C) and warm (44°C) water (Variotherm Plus; Atmos, Allentown, PA, USA). Nystagmus was analyzed quantitatively with a VisualEyes system (Micromedical, Chatham, IL, USA). Unilateral vestibular hypofunction was confirmed when canal paresis [CP=|right side response-left side response|/(right side response+left side response)] was ≥25%.

cVEMP was recorded using the method described previously [9,10]. Briefly, surface myogenic potential was record-

ed from the ipsilateral sternocleidomastoid (SCM) muscle with a Navigator Pro system (Bio-Logic, Mundelein, IL, USA) in the supine position with elevation of the head from the bed without rotation [9]. Active, reference, and ground electrodes were placed on the mid-portion of the SCM muscle, sternum, and forehead, respectively. Using an in-ear earphone, 500 Hz alternating air conducted sound tone-burst stimulation was delivered at 90 dB nHL. The rise/fall time was 1 ms, the plateau time was 2 ms, and the repetition rate was 5.1 Hz. Background electromyography activity of the SCM muscle was not recorded, although an optimal positioning technique for eliciting consistent cVEMP responses was used [11-13]. oVEMP was recorded in the sitting position with the eyes gazing upwards (30°). Active, reference, and ground electrodes were placed below the contralateral eye, 1−3 cm below the active electrode, and on the forehead, respectively. Using an in-ear earphone, 500 Hz rarefaction air conducted sound tone-burst stimulation was delivered at 90 dB nHL with a Navigator Pro system. The rise/fall time was 1.5 ms with no plateau and the repetition rate was 5.1 Hz. The interaural amplitude difference (IAD) ratio was obtained using the following formula: (Rt side amplitude-Lt side amplitude)/(Rt side amplitude+Lt side amplitude). The IADs were considered abnormal if the measurement value was >0.25 [9,10]. The VEMP was also considered abnormal when there was no detectable response with stimulus at 90 dB HL.

SVV was measured with a laser light bar lid from a distance of 1 m in a completely dark room using a System 2000 Auto-Traverse Rotational Vestibular Chair (Micromedical). The subject was instructed to rotate the laser light bar until it was completely vertical. The angulation between the subject's perceived vertical orientation and true vertical was measured. Four responses were averaged, with the preset angle to the left side twice and to the right side twice [14]. SVV was considered abnormal when it deviated by >2.5° [15]. The site of pathology and extent of otolith dysfunction were determined according to the cVEMP, oVEMP, and SVV tests. The saccule was presumed to be involved when cVEMP response was abnormal. The utricle was presumed to be involved when the oVEMP and/or SVV were abnormal. Both the utricle and saccule were presumed to be involved when cVEMP response was abnormal and the oVEMP and/or SVV were abnormal.

For vHIT, the right eye was recorded with an ICS Impulse system (GN Otometrics, Taastrup, Denmark). All three canals were evaluated in most patients, but only the horizontal canals were evaluated in some subjects who were unable to cooperate. The subjects were instructed to gaze at a target at a distance of 1.5 m. The eye position was calibrated using laser targets projected forward from the goggles. Head impulses were conducted from the back of the subject to each side with unpredictable and abrupt timing and direction. At least 10−20 impulses were recorded for each direction. The velocity of the head rotation was targeted between 100°/s and 300°/s. The system calculated the gain using the area under the curve (AUC) method (eye velocity AUC/head velocity AUC) [4]. Gain in the horizontal canal <0.8 was considered abnormal [16]. The presence of catch-up saccade was also examined. Overt and covert saccades were regarded as clinically significant catch-up saccades when the velocity exceeded 100°/s [16].

mCTSIB was performed using a Basic Balance Master (NeuroCom International Inc., Clackamas, OR, USA) according to the manufacturer's protocol [17,18]. Briefly, subjects were asked to stand with the arms across the chest in each of the four test conditions: EO firm, standing on a firm surface with the eyes open; EC firm, standing on a firm surface with the eyes closed; EO foam, standing on a compliant foam surface with the eyes open; EC foam, standing on a compliant foam surface with the eyes closed. The amount of sway represented by perturbation in the center of pressure was recorded. The response for each condition was considered abnormal when the amount of sway exceeded the limit of age- and height-matched normative reference values provided by the manufacturer.

Statistical analysis

All data are expressed as means±standard deviation. Nonparametric Mann-Whitney U test and chi-squared test (or Fischer's exact test) were used for analysis of continuous and categorical variables, respectively. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA), and $p<0.05$ was taken to indicate statistical significance.

Results

The demographics of the lab- & Sx-based iOD group and the lab-based iOD group are shown in Table 1. The lab-based iOD group was approximately 15 years older than the lab- & Sx-based iOD group. The majority (66.7%) of patients in the lab-based iOD group were over 60 years old, while only one patient (9.1%) was over 60 in the lab- & Sx-based iOD group ($p=0.009$) (Fig. 1). There were no significant differences in gender ratio, frequency of vertigo attacks, duration of illness, or severity of dizziness NRS score between the two groups. All patients in the lab-based iOD group had spinning vertigo as their chief symptom, while all patients in the lab- & Sx-

based iOD group had otolith organ-related vertigo (p<0.001). Patients in the lab- & Sx-based iOD group described their symptoms as a horizontal floating sensation (n=7), flipping upside down (n=2), lateral translation (n=1), or up-down vibration (n=1). The utricle was the most frequently involved otolith organ (75.0−81.8%). Utricle involvement without saccular involvement was found in 50.0−54.5% of cases, while both the utricle and saccule were involved in 25.0−27.3% of the patients. There was no significant difference between the two groups in terms of extent of involvement.

Clinical diagnosis was idiopathic in 81.8% of cases in the lab- & Sx-based iOD group (Table 2). That is, taking the symptoms and VFT findings together, the diagnosis did not correspond to any currently known vestibular disorder. Accordingly, the final diagnosis was idiopathic iOD. The clinical diagnosis was idiopathic iOD in only 16.7% of cases in the lab-based iOD group, which was a significantly lower incidence than that in the lab- & Sx-based iOD group (p=0.003). The most common combined vestibular disorder accompanying iOD consisted of benign paroxysmal positional vertigo (BPPV) and Ménière's disease (MD).

The vHIT gain was normal in both ears in all subjects ex-

Table 1. Demographics of participants divided into two groups according to their symptoms

	Lab- & Sx-based iOD	Lab-based iOD	*p*-value
No. of subjects	11	12	
Age (years)	42.5±20.5	58.5±13.0	0.009†
Frequency of attack (median, /mo)	4.3	0.6	0.970
Dizziness severity NRS	2.7±2.5	2.5±2.3	0.913
Duration of illness (mo)	50.3±70.9	49.5±87.3	0.758
Dizziness character			<0.001
Spinning vertigo*	0	12	
Non-spinning vertigo*	11	0	
Horizontal floating	7 (63.6)	0	
Flip upside down	2 (18.2)	0	
Lateral translation	1 (9.1)	0	
Up-down vibration	1 (9.1)	0	
Site of pathology			0.925
Utricle involved	6 (54.5)	6 (50.0)	
Saccule involved	2 (18.2)	3 (25.0)	
Utricle and saccule involved	3 (27.3)	3 (25.0)	

Data are expressed as mean±standard deviation or number (%). *Definition of vestibular symptoms according to the first International Classification of Vestibular Disorders of the Barany Society [8], †Cross-tab analysis: >60 years old vs. <60 years old. iOD: isolated otolith dysfunction, NRS: numeric rating scale on severity of dizziness symptoms at 2−4 months post-treatment (10, worst possible dizziness ever experienced; 0, no dizziness), duration of illness: time from the first dizziness attack to performing vestibular function test

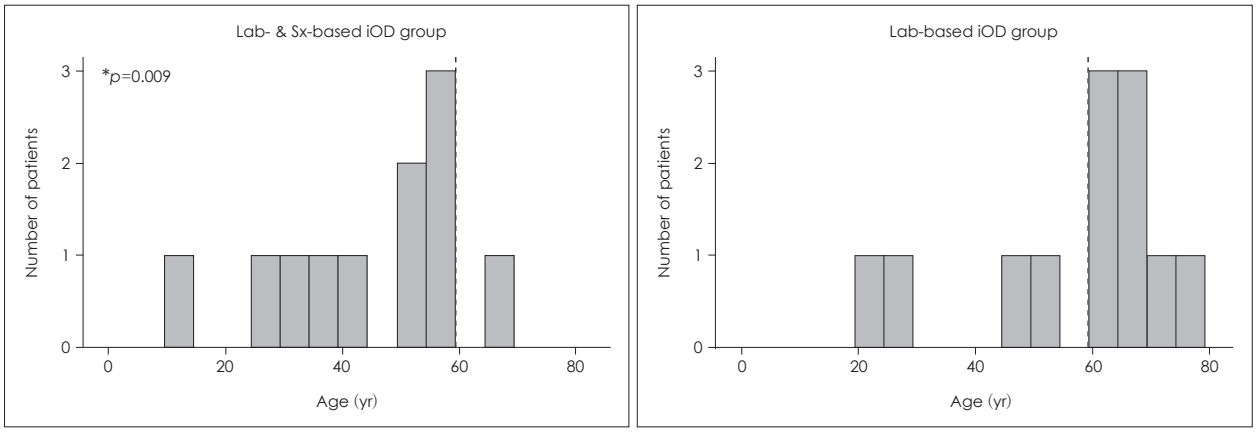

Fig. 1. Differences in age distribution between lab- and symptom (Sx)-based isolated otolith dysfunction (iOD) group and lab-based iOD group. The lab-based iOD group (58.5±13.0 years old) was approximately 15 years older than the lab- & Sx-based iOD group (42.5±20.5 years old). Only one patient (9.1%) was >60 years old the lab- & Sx-based iOD group, while the majority (66.7%) of those in the lab-based iOD group were >60 years old (p=0.009).

cept in one ear of one subject in the lab-based iOD group (left horizontal canal gain was 0.7 in this subject). The gain was normal in all subjects in the lab- & Sx-based iOD group. Catch-up saccades were found in 54.5% of patients in the lab-based iOD group. No catch-up saccades were detected in the lab- & Sx-based iOD group. The detection rate of catch-up saccades was significantly higher in the lab-based iOD group than the lab- & Sx-based iOD group (p=0.012) (Table 3).

More patients in the lab-based iOD group showed abnormal sway (72.8%) during mCTSIB compared to the lab- & Sx-based iOD group (45.5%). In particular, the EC foam condition (the most sensitive condition for detecting vestibular dysfunction) was abnormal in 45.5% of patients in the lab-based iOD group. Although higher than that of the lab- & Sx-based iOD group (27.3%), the difference was not statistically significant (Table 3).

Discussion

The imperfect sensitivity and specificity of the caloric test can be a critical problem when defining iOD. The general definition of iOD is "abnormal function of the otolith organs despite the normal function of the semicircular canals." In most studies reported to date, the caloric test was used as the gold standard to confirm normal function of the SCC [1-3, 7,12,19]. The validity of this definition is dependent on the sensitivity and specificity of the caloric test [20]. However, the caloric test cannot be used to evaluate the superior and posterior canal function. It is also limited by the fact that caloric irrigation presents a low-frequency stimulus to the labyrinth [20]. The sensitivity was evaluated according to the time delay from onset of vestibular neuritis, and was shown to be 100% up to 2 weeks, 80−85% up to 1 month, 75% at 3−6 months, and 65% at 12 months [21]. That is, symmetric ca-

Table 2. Clinical diagnosis of subjects with iOD

Clinical diagnosis	Lab- & Sx-based iOD group (n=11)	Lab-based iOD group (n=12)
iOD without other vestibular disorder	9 (81.8)	2 (16.7)
Idiopathic iOD of utricle (Ut)	5 (45.5)	1 (8.3)
Idiopathic iOD of saccule (Sa)	1 (9.1)	0 (0.0)
Idiopathic iOD of Ut and Sa	3 (27.3)	1 (8.3)
iOD combined with other vestibular disorders	2 (18.2)	10 (83.3)
iOD+BPPV	1 (9.1)	6 (50.0)
iOD+SSNHL	1 (9.1)	0 (0.0)
iOD+MD	0 (0.0)	3 (25.0)
iOD+vestibular paroxysmia	0 (0.0)	1 (8.3)

Data are expressed as number (%). Cross-tab analysis: iOD without other vestibular disorders vs. iOD combined with other vestibular disorders (p=0.003). iOD: isolated otolith dysfunction, definition of iOD was 1) normal caloric response and 2) abnormal otolith function test (cVEMP or oVEMP or SVV), BPPV: benign paroxysmal positional vertigo, SSNHL: sudden sensorineural hearing loss, MD: Ménière's disease

Table 3. Vestibular function test findings

	Lab- & Sx-based iOD group (n=11)	Lab-based iOD group (n=12)	p
Videonystagmography			
Spontaneous nystagmus	0 (0)	1 (8.3)	0.740
Caloric test			
Canal paresis (%)	7.6±7.2	10.2±6.0	0.366
Video head impulse test			
Number of patients	10	11	
Presence of catch-up saccade	0 (0)	6 (54.5)	0.012*
Gain (right ear)	1.00±0.12	1.01±0.13	0.972
Gain (left ear)	1.01±0.12	1.02±0.17	0.833
Modified Clinical Test of Sensory Interaction on Balance			0.427
Number of patients	11	11	
Normal	6 (54.5)	3 (27.3)	
Abnormal sway in EC foam (vestibular pattern)	3 (27.3)	5 (45.5)	
Abnormal sway in EC firm (somatosensory pattern)	2 (18.2)	3 (27.3)	

Data are expressed as mean±standard deviation or number (%). *Fischer's exact test. iOD: isolated otolith dysfunction, EC foam: test conditions with eyes closed and standing on a foam pad, EC firm: test conditions with eyes closed and standing on firm floor

loric responses did not exclude the possibility of canal dysfunction a few months after the onset of vestibulopathy [20]. Considering the possibility of false negative results in the caloric test, it can be assumed that several months after onset of vertigo some subjects will be misdiagnosed as iOD despite SCC involvement. That is, a significant proportion of subjects in the lab-based iOD group may actually not have represented true iOD. The identification of vHIT catch-up saccades in more than half of the patients in the lab-based iOD group may support this hypothesis.

There are two possible interpretations for the vestibular disorders accompanying iOD, i.e., the accompanying vestibular disorder may have a causal relationship with iOD, or may simply be a bystander that is not directly related to iOD. The most common accompanying vestibular disorder was BPPV in this study, as also reported by other authors [1]. Utricular dysfunction has been suggested as a possible mechanism of BPPV [7]. For example, it has been reported that patients with BPPV have a tendency to show abnormal oVEMPs more frequently than cVEMPs [22]. We also found that BPPV was more frequently accompanied by utricular dysfunction [oVEMP or SVV abnormality, 5/7 patients (71.4%)] than saccular dysfunction [cVEMP abnormality, 2/7 patients (28.6%)]. Considering the anatomy of the inner ear, it is strongly suggested that the detached otolith debris of BPPV originates from the utricle. In this sense, iOD (more specifically utricular dysfunction) may be the cause of detached otolith debris and, consequently, the cause of BPPV. On the other hand, BPPV and iOD may have no causal relationship in some patients. Incidental comorbidity is plausible considering the high prevalence of BPPV. For example, in our patients, BPPV did not occur at the same time point as iOD. Considering the time difference between the onset of BPPV and the onset of iOD symptoms, it is unlikely that iOD was a direct cause of BPPV. MD was also a frequent vestibular disorder accompanying iOD in this study and in that reported by Iwasaki, et al. [7]. Endolymphatic hydrops in the saccule and utricle may explain the abnormal findings of cVEMP and oVEMP. That is, in some cases, MD may be a cause of otolith dysfunction. Approximately half of all MD patients are thought to show abnormal cVEMPs and/or oVEMPs during the quiescent period [7]. In addition, a human temporal bone study showed endolymphatic hydrops in the saccule and utricle [23]. In our case series, it was not clear whether the accompanying vestibular disorder (BPPV or MD) was the cause of iOD or merely a bystander. However, as there can be a causal relationship between the accompanying vestibular disorder and otolith dysfunction, we may not be able to classify these patients as idiopathic iOD.

One problem in classifying lab- & Sx-based iOD is that it is still not clear which symptoms are characteristic of otolith dysfunction. Vestibular symptoms caused by otolith dysfunction have traditionally been suggested as a tilting sensation, a sense of moving to and fro, lateropulsion, or feelings of falling [7]. Furthermore, swaying, rocking [12], tilting, a pulling sensation in the anteroposterior direction, and a somatosensory illusion of walking on pillows or on uneven ground were suggested to originate from otolith organ dysfunction [19]. Recurrent drop attacks also represent a well-known symptom characteristic of otolith organ dysfunction [19]. Previous studies revealed cVEMP abnormalities in MD patients with vestibular drop attacks [1]. Human histopathological studies have found damaged otolithic membranes in the utricle in patients who have had multiple episodes of Tumarkin's drop attacks [24,25]. However, our cohort included no iOD patients with repeated drop attacks. Fujimoto, et al. [1] reported that only one of 28 iOD patients experienced repeated drop attacks. It seems that intuitive pathophysiological assumptions about iOD are not always consistent with the actual clinical symptoms. That is, it may be difficult to define otolith-specific symptoms. However, to classify the lab- & Sx-based iOD correctly, spinning vertigo should be strictly excluded from the otolith-specific symptoms.

The observations outlined above raise questions about how the utricle and/or saccule can become compromised while other parts of the vestibule, especially the SCCs, remain intact. The pathophysiology of iOD has not been elucidated [2]. Based on the differential blood supply and innervation patterns, it is possible for a vestibular disorder to involve only a portion of the peripheral vestibular apparatus [26]. One hypothesis is that viral activation can involve a selected portion of the inner ear or selective segment of the vestibular nerve without involving other parts of the inner ear. It has been reported that vestibular neuritis does not necessarily affect the complete labyrinth, but can involve only partial loss of vestibular function [27]. The patients with lab- and Sx-based iOD in this study may correspond to this observation, indicating that even more specific lesions of the otolith organs can occur. With regard to other possibilities, Schuknecht [28] reported experimental degeneration of otolith membrane by cutting the anterior vestibular artery. Selective hydrops of the utricle and/or saccule can also be responsible for iOD. It has been reported that the otolith organs develop endolymphatic hydrops more frequently than the SCCs [23]. In addition, a mathematical model showed that the SCCs are most resistant to hydropic expansion, while the saccule is most vulnerable [29]. Although the precise pathophysiology of iOD is not clear, previous observations indicated that selective vestibulopathy of the utricle and/or saccule may be possible.

Table 4. Proposal of diagnostic criteria for iOD and summary of the basis of classification from four studies

	Murofushi, et al [2]	Pelosi, et al [5]	Fujimoto, et al [1]	This study	
Diagnostic terms used by the authors					
Term	Idiopathic otolithic vertigo (IOV)	Isolated utricular dysfunction (iUD)	Otolith organ-specific vestibular dysfunction (OSVD)	Lab-based iOD	Lab- and Sx-based iOD
Lab criteria	NR	Abnormal oVEMP and normal cVEMP <and> normal caloric or SHA	Abnormal cVEMP or oVEMP <and> normal caloric and vHIT	Abnormal cVEMP, oVEMP, or SVV <and> normal caloric	
Symptom criteria	1) Episodic lateral tilting or translational sensations 2) Episodic anteroposterior tilting or translational sensations 3) Episodic up-down translational sensations	NR	NR	NR	1) Horizontal floating 2) Flip upside down 3) Lateral translation 4) Up-down vibration
Demographics and clinical characteristics					
Number of subjects	16	31	28	23	
Age (mean years)	42.5 (15–68)	48±14	58.7±15.8	58.5±13.0	42.5±20.5
Gender (M:F)	6:10	9:22	12:14	3:9	3:8
Prevalence of spinning vertigo as the symptom	0% (0/16)	55% (17/31)	75% (21/28)	100% (12/12)	0% (0/11)
Involved otolith organ (Ut:Sa:both)	4:12:0 Classified by cVEMP frequency preference	31:0:0 Classified by cVEMP & oVEMP	14:5:9 Classified by cVEMP & oVEMP	6:3:3 Classified by cVEMP, oVEMP, & SVV	6:2:3 Classified by cVEMP, oVEMP, & SVV
Abnormal caloric test	0% (0/11) Murofushi 2013	0% (0/30)	0% (0/28)	0% (0/12)	0% (0/11)
Abnormal vHIT	Not performed	Not performed	0% (0/28)	54.5% (6/11)	0% (0/10)
Accompanying disorder	None	Migraine, BPPV	BPPV, MD	BPPV, MD	Less likely
Proposal on the diagnostic criteria					
Higher level	iOD				
Middle level	Probable iOD				Definite iOD
Lower level	Sx-based iOD	Lab-based iOD			Lab- and Sx-based iOD
Lab criteria	NR	Normal caloric and vHIT <and> Abnormal cVEMP, oVEMP, or SVV			Normal caloric and vHIT <and> Abnormal cVEMP, oVEMP, or SVV
Symptom criteria	Non-spinning, translation, tilt, floating, or flipping over	NR			Non-spinning, translation, tilt, floating, or flipping over

iOD: isolated otolith dysfunction, NR: not required, oVEMP: ocular vestibular evoked myogenic potential, cVEMP: cervical vestibular evoked myogenic potential, vHIT: video head impulse test, SVV: subjective visual vertical, SHA: sinusoidal harmonic acceleration, Ut: utricle, Sa: saccule, BPPV: benign paroxysmal positional vertigo, MD: Ménière's disease, SCC: semicircular canal

Based on the findings of this and other studies, we propose structured diagnostic criteria for iOD (Table 4) consisting of definite iOD and probable iOD. Probable iOD may be further subclassified into Sx-based iOD (as in IOV) and lab-based iOD (as in OSVD) to indicate the rationale for making a diagnosis of iOD. Definite iOD requires both lab findings and symptom characteristics consistent with iOD (lab- & Sx-based iOD). Lab- & Sx-based iOD (definite iOD) may be considered as the only pure or true iOD. Probable iOD allows for some degree of uncertainty. For example, Sx-based iOD may be debated because there is currently no consensus on which symptoms are pathognomonic for otolith dysfunction. The lab-based iOD may also be classified as probable iOD and not definite iOD because, in some cases, vestibulopathy involving the SCC may be misclassified into this group due to the insensitive caloric test outcome. The definition of OSVD in the study by Fujimoto, et al. [1] was similar to the lab-based iOD group in the present study. As shown in Table 4, there were many similarities between OSVD and the lab-based iOD group. Age, gender, prevalence of spinning vertigo as symptoms, inner ear organ involvement, and accompanying vestibular disorders were similar between the two studies. These clinical similarities were the basis of classifying lab-based iOD into one category. Meanwhile, the clinical presentations were quite different when compared to definite iOD. Therefore, we should differentiate probable iOD from definite iOD. If the etiology of definite iOD is not clear, it may be indicated as "idiopathic definite iOD." If an accompanying vestibular disorder, such as MD, is presumed to be the cause of iOD, it may be referred to as "secondary definite iOD." We hope that the new definition of definite iOD will help researchers to identify patients who are more likely to be true cases of iOD, and facilitate comparisons of results between different studies.

In conclusion, we screened for patients who had vestibular symptoms and showed abnormal cVEMP, oVEMP, or SVV without canal paresis. Dizziness can be attributed to an otolith organ-specific (isolated) disorder, and iOD may be a distinct cause of dizziness in these cases. Although the lab findings were similar in iOD patients, patients with otolith-specific symptoms (lab- & Sx-based iOD group) and without otolith-specific symptoms (lab-based iOD group) may be different. We found clear differences between the lab-based iOD group and the lab- & Sx-based iOD group in terms of subjective dizziness sensation, age, accompanying vestibular disorder, and detection rate of catch-up saccade during vHIT. Based on these results and those of previous studies, we propose structured diagnostic criteria for iOD consisting of definite iOD and probable iOD. Definite iOD requires both lab findings and symptom characteristics consistent with iOD (lab- and Sx-based iOD). Strictly speaking, lab- and Sx-based iOD may be considered as the only pure or true iOD. Probable iOD allows for some uncertainties, such as inconsistent symptoms or inconsistent lab findings. We hope that the new definition of definite iOD will help researchers to identify patients who are more likely to have true iOD, and facilitate comparisons of results between different studies.

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Conflicts of interest

The authors have no financial conflicts of interest.

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