Auris Nasus Larynx 48 (2021) 400–407

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Patients with vertigo/dizziness of unknown origin during follow-ups by general otolaryngologists at outpatient town clinic

Daisuke Nishikawa, Yoshiro Wada, Tomoyuki Shiozaki, Masayuki Shugyo, Taeko Ito, Ichiro Ota, Tadashi Kitahara*

Department of Otolaryngology-Head and Neck Surgery, Nara Medical University,840 Shijo-cho, Kashihara, Nara 634-8522, Japan

ARTICLE INFO

Article history:
Received 4 May 2020
Accepted 16 September 2020
Available online 3 October 2020

Keywords:
Outpatient town clinic
Unknown origin
Motion-evoked floating sensation
No obvious nystagmus
Benign paroxysmal positional vertigo
Orthostatic dysregulation

ABSTRACT

Objectives: The purpose of this study was to access the contribution of vertigo/dizziness-related patients' interview and examinations during short-term hospitalization in determining the accurate final diagnosis of vertigo/dizziness of unknown origin.

Methods: We reviewed 1905 successive vertigo/dizziness patients at the Vertigo/Dizziness Center of Nara Medical University, who were introduced from general otolaryngologists at outpatient town clinic from May 2014 to April 2020. However, 244 patients were diagnosed with vertigo/dizziness of unknown origin (244/1905; 12.8%). Of these patients, 240 were hospitalized and underwent various examinations, including caloric test (C-test), video head impulse test (vHIT), vestibular evoked cervical myogenic potentials (cVEMP), subjective visual vertical (SVV), inner ear magnetic resonance imaging (ieMRI), Schellong test (S-test), and self-rating questionnaires of depression score (SDS).

Results: According to the examination data, together with interviewed vertigo/dizziness characteristics and daily changeable nystagmus findings, the final diagnoses were as follows: benign paroxysmal positional vertigo (BPPV: 107/240; 44.6%), orthostatic dysregulation (OD: 56/240; 23.3%), vestibular peripheral disease (VPD: 25/240; 10.4%), vestibular migraine (VM: 14/240; 5.8%), Meniere's disease (MD: 12/240; 5.0%), gravity perception disturbance (GPD: 10/240; 4.2%), psychogenic vertigo (Psycho: 10/240; 4.2%), and unknown (Unknown: 6/240; 2.5%). Supporting factors of final diagnosis was seen in gender, evoked dizziness, and positional nystagmus as BPPV; in evoked dizziness, S-test, and hypertension as OD; in evoked dizziness, head shaking after nystagmus, C-test, and vHIT as VPD; in gender, headache, and S-test as VM; in ear fullness and ieMRI as MD; in gender, evoked dizziness, and SVV as GPD; and in SDS as Psycho. To sum up, the ratios of Unknown were significantly reduced by this short-term hospitalization (244/1905→6/240).

Conclusions: The answer lists for vertigo/dizziness of unknown origin obtained in the present study may be helpful for future general otolaryngologists at outpatient town clinic to better attain an accurate final diagnosis.

* Corresponding author.
E-mail address: tkitahara@naramed-u.ac.jp (T. Kitahara).

https://doi.org/10.1016/j.anl.2020.09.012
0385-8146/

1. Introduction

Lists of statistical surveys of vertigo/dizziness disease show differences between outpatient Otolaryngology and Neurology clinics. Generally, benign paroxysmal positional vertigo (BPPV) is the most common followed by Meniere's disease (MD), vestibular neuritis (VN), and sudden deafness with vertigo (SDV) at ENT departments [1–3]. However, BPPV is most common followed by VN, vestibular migraine (VM), and orthostatic dysregulation (OD) at the Department of Neurology [4,5]. This discrepancy may be explained by patients with hearing disturbance such as MD and SDV choosing to see ENT doctors rather than neurologists. Additionally, 10%-15% of patients are diagnosed with vertigo/dizziness of unknown origin [1–5].

At outpatient town clinics, general otolaryngologists often diagnose vertigo/dizziness using limited time for patients' interview and limited otology/neurotology examinations, resulting in higher diagnosis of vertigo/dizziness of unknown origin. Accurate diagnosis is essential for physicians to select an appropriate therapeutic strategy to promptly cure a disease. In this study, we have focused on the contribution of vertigo/dizziness-related patients' interview and examinations during short-term hospitalization in the accurate final diagnosis of vertigo/dizziness of unknown origin.

2. Materials and methods

This clinical study was registered with UMIN (identification number: 000018399) and was approved by the Ethics Committee of Nara Medical University Hospital (identification number: 0889).

2.1. Patients

We reviewed 1905 successive vertigo/dizziness patients at the Vertigo/Dizziness Center of Nara Medical University, who were introduced from general otolaryngologists at outpatient town clinic from May 2014 to April 2020 (Fig. 1). Most patients were definitely diagnosed with BPPV, MD, VN, SDV, OD, or VM in accordance with the diagnostic guideline of the International Classification of Vestibular Disorder (ICVD) in 2015 [6–10]. However, 244 patients were diagnosed with vertigo/dizziness of unknown origin (244/1905; 12.8%) during follow-ups at the outpatient clinic. Of these patients, 240 patients were hospitalized and underwent various examinations, including caloric test (C-test), vestibular evoked cervical myogenic potentials (cVEMP), subjective visual vertical (SVV), inner ear magnetic resonance imaging (ieMRI), Schellong test (S-test), and self-rating questionnaires of depression score (SDS).

Among the 240 cases hospitalized for accurate final diagnosis, 92 were males and 148 were females, with a mean age of 52.5 ± 15.6 years. The average duration from the day of onset to the day of hospitalization was 38.3 ± 20.2 months. We determined the duration of vertigo/dizziness of unknown origin according to the patients' history of subjective vertiginous sensation; we were unable to accurately count the number of vertigo attacks as symptoms included motion-evoked floating sensation.

2.2. Evaluations

2.2.1. Otology/neurotology tests

The C-test was used to assess lateral semicircular-canal function on both sides of the head as an alternative brief version [11,12]. Cold water (20°C; 20 mL) was injected into the external auditory meatus over the course of 10 s in turn, and the induced nystagmus was recorded with electronystagmography (ENG). The test was performed in the dark, with the patient's eyes open. Based on the maximum slow-phase eye velocity, CP in the c-test was classified as positive when the ENG response was ≤10 deg/s.

In addition, the vHIT was used to assess the function of the three semicircular canals, including the lateral one. Three-dimensional vHIT was performed to assess the vestibulo-ocular reflex (VOR) in the three semicircular canal planes using a lightweight video-oculography device (ICS Impulse; GN Otometrics, Taastrup, Denmark) with an integrated digital high-speed camera designed for quantitative HIT testing. Experienced otologists performed brief, abrupt, and unpredictable head rotations on patients. At least 20 impulses with peak velocity ranges of 100-250 s were collected from each canal. Individual VOR gains were automatically calculated as the ratio of the area under the entire eye-velocity response divided by the area under the entire head-velocity stimulus using the device software (OTOsuite vestibular software, version 4.00, build 1286; GN Otometrics). It was assumed that the normal VOR gains were 0.8 or more for horizontal canals. We considered patients whose VOR gains were less than the cutoff to have CP. When catch-up saccades (CUS) with amplitudes comparable to the amplitude of the head movements were detected simultaneously, CP in vHIT was classified as positive at the time of low gain with CUS [13]. cVEMP was used to assess saccule and inferior vestibular primary afferent neuron function. Electrodes were placed on the upper half of each sternocleidomastoid muscle, with a reference electrode placed on the lateral end of the upper sternum and a ground electrode placed on the nasion. During the recording procedure, the subjects were asked to lie in a supine position and raise their heads to contract the sternocleidomastoid muscle. For acoustic stimuli, air conducted at 500 Hz and 1000 Hz STBs (125 dB SPL, rise/fall time = 1 ms, plateau time = 2 ms) was presented through headphones at a 5-Hz stimulation rate. The signals were amplified and bandpass filtered (20-2000 Hz), and 100 responses were averaged. The time window for the recording was -20 to 80 ms. Two runs were performed for each ear to confirm data reproducibility. The first biphasic responses (p13-n23) produced by the sternocleidomastoid muscle ipsilateral to the stimulated ear were assessed. To eliminate the effects of variations in muscle activity, the mean background amplitude was calculated from the mean rectified background activity during the 20 ms prestimulus period. In the present study, the right-left or left-right ratios in the activity ≤0.5 were considered positive [14].

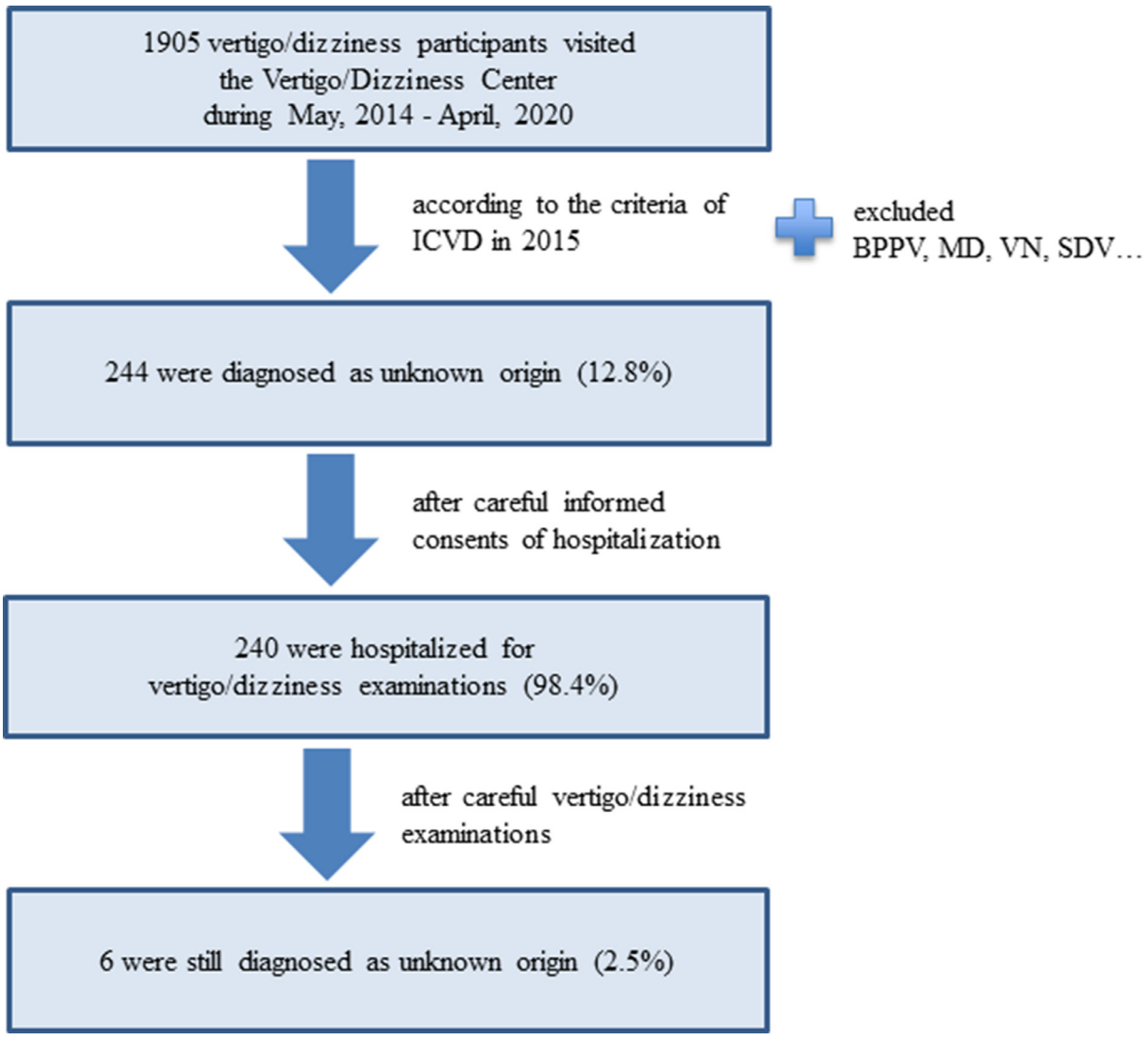

Fig. 1. Flow chart of the case enrollment
We examined 1905 successive vertigo/dizziness patients at the Vertigo/Dizziness Center in the Nara Medical University, who were introduced from general otolaryngologists at outpatient town clinic during May 2014 to April 2020. Most patients were definitely diagnosed with benign paroxysmal positional vertigo (BPPV), Meniere's disease (MD), vestibular neuritis (VN), and sudden deafness with vertigo (SDV) in accordance with the diagnostic guideline of the International Classification of Vestibular Disorder (ICVD) in 2015. However, 244 patients were diagnosed as vertigo/dizziness with unknown origin during the follow-up process at the outpatient clinic. Two hundred and forty were enrolled to be hospitalized and underwent various kinds of vertigo/dizziness related examinations.

SVV was used to assess otolith organ function (i.e., the gravity sensitivity functioning test) with the bucket method. A clean, opaque, white, plastic bucket (38 cm deep, 23 cm diameter) was converted to a test device by marking a 15 cm black line centered on the inner bottom and placing a protractor on the outer bottom aligned with the marked inner line. A small weight was hung from the center of the protractor. The bucket was placed on its side on a table (29.5 × 25 cm) atop a height-adjustable tripod to stabilize the bucket in pitch and yaw. In that position, when the bucket was rolled in the clockwise and counterclockwise directions, the string and weight rotated freely so that the investigator could read the protractor. Prior to testing, the height of tripod was adjusted so that each subjects' face fit easily into the bucket. All measurements were taken by the examiner, monocularly, using the examiner's dominant eye. Two test conditions were used in random order: vertical roll from the upper end of the line, and right and left roll of 0°. Subjects were given three trials per condition. The starting point for each trial was selected randomly and varied from 10-20° from the 0° line. Before each trial, the subject was instructed to state when the line was vertical while the examiner moved the bucket. In the present study, the angle gaps outside of the range between -2.0° (left) and +2.0° (right) were considered positive [15].

2.2.2. *Imaging tests*

Performing ieMRI at 4 h after intravenous administration of Gadolinium was previously reported to be useful for EH imaging [16]. In the present study, all patients underwent heavy T2-weighted MRI cisternography for an anatomical reference of the total lymph fluid, heavy T2-weighted (hT2W) three-dimensional fluid-attenuated inversion recovery

Table 1. Background and subjective symptoms of patients with vertigo/dizziness.

Diagnosis	BPPV	OD	VPD	VM	MD	GPD	Psycho	Unknown	Stat
Number (n=240)	n=107	n=56	n=25	n=14	n=12	n=10	n=10	n=6	chi-square p-value
M/F (male/female)	30 / 77	30 / 26	14 / 11	4 / 10	6 / 6	2 / 8	4 / 6	2 / 4	16.4 0.022
Age (yr)	56.2 ± 16.5	48.6 ± 24.1	52.8 ± 15.3	42.0 ± 12.9	43.5 ± 15.8	52.4 ± 12.7	34.8 ± 11.5	46.2 ± 16.7	N/A
Duration (mo)	40.3 ± 21.2	38.0 ± 22.6	36.6 ± 18.8	22.5 ± 17.5	20.2 ± 20.0	42.1 ± 22.8	45.6 ± 16.7	42.2 ± 20.7	N/A
Evoked dizziness	107 / 107	56 / 56	25 / 25	5 / 14	9 / 12	10 / 10	0 / 10	2 / 6	169.6 0.00030
Rotatory vertigo	10 / 107	0 / 56	0 / 25	10 / 14	4 / 12	0 / 10	0 / 10	0 / 6	15.1 0.052
Headache	12 / 107	16 / 56	0 / 25	14 / 14	2 / 12	1 / 10	1 / 10	1 / 6	72.5 0.00047
Ear fullness	4 / 107	2 / 56	0 / 25	0 / 14	8 / 12	0 / 10	0 / 10	1 / 6	81.6 0.00064

All the patients' background and subjective symptoms are shown.
BPPV: benign paroxysmal positional vertigo, OD: orthostatic dysregulation, VPD: vestibular peripheral disease, VM: vestibular migraine, MD: Meniere's disease, GPD: gravity perception disturbance, Psycho: psychogenic vertigo, Unknown: unknown origin: Stat: statistical analysis, yr: years, mo: months.

sequences with a 2250 ms inversion time for positive perilymph images, and heavy T2-weighted three-dimensional inversion recovery with a 2050 ms inversion time for positive endolymph images. After image acquisition, a hybrid image of the reversed image of the positive endolymph signal and the negative image of the positive perilymph signal after motion correction by subtracting the positive endolymph images from positive perilymph images were obtained. In this protocol, pixels with a negative value were estimated as representing EH.

Two otolaryngologists blinded to the clinical progress of the patients evaluated the ieMRI findings. If their evaluations differed, a third otolaryngologist made the final decision. The degree of EH was classified as none, mild, or significant, according to criteria reported by Nakashima et al. [17]. When evaluating cochlear EH, we used one axial slice near the modiolus. When evaluating vestibular EH, we used one axial slice that displayed the maximum extent of the vestibule, while the ampulla of the semicircular canal was excluded from evaluation.

Patients with no EH in the vestibule had a ratio of ≤1:3, those with mild EH had a ratio of 1:3-1:2, and those with significant EH had a ratio >1:2. In the present study, both mild and significant EH were defined as 'positive'.

2.2.3. Schellong tests

Daily autonomic status can easily be measured in the clinic using the S-test to check the changes in blood pressure (BP) or pulse rate (PR) as patients stand up from the supine position. The positive range was defined as a systolic BP decrease of >21 mmHg and/or a PR increase of >21 beats/min before and just after standing.

2.2.4. Depression tests

Questionnaires included the SDS which consist of 10 positively and 10 negatively worded items that enquire about depression symptoms. These scores were used to define categories of depression, as follows: not having significant depression (≤40 points) or having significant depression (≥41 points). Patients with SDS scores >40 (possible range 20-80) were classified as having depression. The SDS has been translated into Japanese and the validity of the Japanese version previously confirmed [18].

2.3. Diagnosis

According to the detailed examination results, together with carefully interviewed vertigo/dizziness characteristics and daily changeable nystagmus findings during short-term hospitalization, 240 patients with initial vertigo/dizziness of unknown origin were eventually diagnosed with BPPV, OD, VPD, VM, MD, GPD, Psycho, and Unknown [6–10]. In the present study, the most main vertigo/dizziness disease was selected to make a diagnose, if two or more diseases were overlapped. Therefore, in the present study, patients were diagnosed as VPD by at least one vestibular peripheral disorder among C-test, vHIT and cVEMP with no other obvious reasons for vertigo/dizziness. Patients were diagnosed as GPD by SVV abnormality with no other obvious reasons for vertigo/dizziness. All the Psycho patients had eventually SDS abnormality with no other obvious reasons for vertigo/dizziness. Unknown was defined as patients with no abnormal examination results even after hospitalization.

2.4. Statistical analysis

Chi-square tests (mxn then 2 × 2) were used to determine significant differences between patient groups in terms of their background information, such as gender, subjective symptoms (Table 1), and examination/questionnaire data (Table 2).

All reported p-values were two-sided and those under 0.05 were considered significant. All statistical analyses were performed through SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Table 2. Examination results during short-term hospitalization in patients with vertigo/dizziness.

Diagnosis	BPPV	OD	VPD	VM	MD	GPD	Psycho	Unknown	Stat
Number (n=240)	n=107	n=56	n=25	n=14	n=12	n=10	n=10	n=6	chi-square p-value
Nystagmus	40 / 107	5 / 56	11 / 25	0 / 14	2 / 12	0 / 10	0 / 10	0 / 6	35.8 0.00080
Abnormal C-test	14 / 107	2 / 56	8 / 25	0 / 14	2 / 12	0 / 10	0 / 10	0 / 6	20.5 0.0046
Abnormal vHIT	10 / 107	2 / 56	20 / 25	0 / 14	0 / 12	0 / 10	0 / 10	0 / 6	110.2 0.00082
Abnormal cVEMP	12 / 107	2 / 56	5 / 25	0 / 14	2 / 12	0 / 10	0 / 10	0 / 6	11.4 0. 12
Abnormal SVV	40 / 107	6 / 56	2 / 25	2 / 14	2 / 12	10 / 10	0 / 10	0 / 6	48.4 0.00029
Abnormal ieMRI	4 / 107	0 / 56	1 / 25	0 / 14	11 / 12	0 / 10	0 / 10	0 / 6	149.2 0.00059
Abnormal S-test	34 / 107	54 / 56	5 / 25	9 / 14	3 / 12	1 / 10	0 / 10	0 / 6	97.8 0.00031
Hypertension	22 / 107	42 / 56	1 / 25	0 / 14	1 / 12	0 / 10	0 / 10	0 / 6	91.5 0.00061
SDS score	35 / 107	18 / 56	2 / 25	2 / 14	2 / 12	2 / 10	10 / 10	0 / 6	35.6 0.00088

Exam data presented as ratios (+) of the number of each disease outside the normal range of the examinations and questionnaires.
BPPV: benign paroxysmal positional vertigo, OD: orthostatic dysregulation, VPD: vestibular peripheral disease, VM: vestibular migraine, MD: Meniere's disease, GPD: gravity perception disturbance, Psycho: psychogenic vertigo, Unknown: unknown origin: Stat: statistical analysis, C-test: caloric test, vHIT: video head impulse test, cVEMP: vestibular evoked cervical myogenic potentials, SVV: subjective visual vertical, ieMRI: inner ear magnetic resonance imaging, S-test: Schellong test, SDS: self-rating questionnaires of depression score.

3. Results

According to the examination data, together with interviewed vertigo/dizziness characteristics and daily changeable nystagmus findings, the final diagnosis were as follows: BPPV (107/240; 44.6%), OD (56/240; 23.3%), vestibular peripheral disease (VPD) (25/240; 10.4%), VM (14/240; 5.8%), MD (12/240; 5.0%), gravity perception disturbance (GPD) (10/240; 4.2%), psychogenic vertigo (Psycho) (10/240; 4.2%), and unknown origin (Unknown) (6/240; 2.5%). All the percentages added up to just 100.0%, because the most main vertigo/dizziness disease was selected to make a diagnose.

All patients' backgrounds and subjective symptoms are shown in Table 1. Otology/neurotology exam data of ieMRI, S-test, and SDS score were presented as ratios (+) of the number of each disease outside the normal range of examinations and questionnaires in Table 2. OD was diagnosed mainly by S-test abnormality along with dizzy symptoms during long-term standing and/or walking in their daily life. SVV abnormality was required for GPD diagnosis and SDS abnormality was essential for Psycho diagnosis. There were no abnormal findings in the present exams in Unknown. The reasons why these 240 patients were originally diagnosed as Unknown at outpatient clinics were considered in Discussion.

The BPPV ratio (+) data were as follows: female/total = 72.0% (77/107), evoked dizziness = 100.0% (107/107), rotatory vertigo = 9.3% (10/107), headache = 11.2% (12/107), ear fullness = 3.7% (4/107), nystagmus = 37.4% (40/107), C-test = 13.1% (14/107), vHIT = 9.3% (10/107), cVEMP = 11.2% (12/107), SVV = 37.4% (40/107), ieMRI = 3.7% (4/107), S-test = 31.8% (34/107), hypertension = 20.6% (22/107), and SDS = 32.7% (35/107). The OD ratio (+) data, female/total = 46.4% (26/56), evoked dizziness = 100.0% (56/56), rotatory vertigo = 0.0% (0/56), headache = 28.6% (16/56), ear fullness = 3.6% (2/56), nystagmus = 8.9% (5/56), C-test = 3.6% (2/56), vHIT = 3.6% (2/56), cVEMP = 3.6% (2/56), SVV = 10.7% (6/56), ieMRI = 0.0% (0/56), S-test = 96.4% (54/56), hypertension = 75.0% (42/56), and SDS = 32.1% (18/56). The VPD ratio (+) data, female/total = 44.0% (11/25), evoked dizziness = 100.0% (25/25), rotatory vertigo = 0.0% (0/25), headache = 0.0% (0/25), ear fullness = 0.0% (0/25), nystagmus = 44.0% (11/25), C-test = 32.0% (8/25), vHIT = 80.0% (20/25), cVEMP = 20.0% (5/25), SVV = 8.0% (2/25), ieMRI = 4.0% (1/25), S-test = 20.0% (5/25), hypertension = 4.0% (1/25), and SDS = 8.0% (2/25). The VM ratio (+) data, female/total = 71.4% (10/14), evoked dizziness = 35.7% (5/14), rotatory vertigo = 71.4% (10/14), headache = 100.0% (14/14), ear fullness = 0.0% (0/14), nystagmus = 0.0% (0/14), C-test = 0.0% (0/14), vHIT = 0.0% (0/14), cVEMP = 0.0% (0/14), SVV = 14.3% (2/14), ieMRI = 0.0% (0/14), S-test = 64.3% (9/14), hypertension = 0.0% (0/14), and SDS = 14.3% (2/14). The MD ratio (+) data, female/total = 50.0% (6/12), evoked dizziness = 75.0% (9/12), rotatory vertigo = 33.3% (4/12), headache = 16.7% (2/12), ear fullness = 66.7% (8/12), nystagmus = 16.7% (2/12), C-test = 16.7% (2/12), vHIT = 0.0% (0/12), cVEMP = 16.7% (2/12), SVV = 16.7% (2/12), ieMRI = 91.7% (11/12), S-test = 25.0% (3/12), hypertension = 8.3% (1/12), and SDS = 16.7% (2/12). In GPD, female/total = 80.0% (8/10), evoked dizziness = 100.0% (10/10), rotatory vertigo = 0.0% (0/10), headache = 10.0% (1/10), ear fullness = 0.0% (0/10), nystagmus = 0.0% (0/10), C-test = 0.0% (0/10), vHIT = 0.0% (0/10), cVEMP = 0.0% (0/10), SVV = 100.0%

(10/10), ieMRI = 0.0% (0/10), S-test = 10.0% (1/10), hypertension = 0.0% (0/10), and SDS = 20.0% (2/10). The Psycho ratio (+) data, female/total = 60.0% (6/10), evoked dizziness = 0.0% (0/10), rotatory vertigo = 0.0% (0/10), headache = 10.0% (1/10), ear fullness = 0.0% (0/10), nystagmus = 0.0% (0/10), C-test = 0.0% (0/10), vHIT = 0.0% (0/10), cVEMP = 0.0% (0/10), SVV = 0.0% (0/10), ieMRI = 0.0% (0/10), S-test = 0.0% (0/10), hypertension = 0.0% (0/10), and SDS = 100.0% (10/10). In Unknown, female/total = 66.7% (4/6), evoked dizziness = 33.3% (2/6), rotatory vertigo = 0.0% (0/6), headache = 16.7% (1/6), ear fullness = 16.7% (1/6), nystagmus = 0.0% (0/6), C-test = 0.0% (0/6), vHIT = 0.0% (0/6), cVEMP = 0.0% (0/6), SVV = 0.0% (0/6), ieMRI = 0.0% (0/6), S-test = 0.0% (0/6), hypertension = 0.0% (0/6), and SDS = 0.0% (0/6).

According to the statistical analysis shown in Table 1 and Table 2, supportive factors for final diagnosis was seen in gender (female: chi-square = 16.4, p = 0.022), evoked dizziness (positive: chi-square = 169.6, p = 0.00030), and positional/positioning nystagmus (positive: chi-square = 35.8, p = 0.00080) as BPPV; in evoked dizziness (positive: chi-square = 169.6, p = 0.00030), S-test (positive: chi-square = 97.8, p = 0.00031), and hypertension (positive: chi-square = 91.5, p = 0.00061) as OD; in evoked dizziness (positive: chi-square = 169.6, p = 0.00030), head shaking after nystagmus (positive: chi-square = 35.8, p = 0.00080), C-test (positive: chi-square = 20.5, p = 0.0046) and vHIT (positive: chi-square = 110.2, p = 0.00082) as VPD; in gender (female: chi-square = 16.4, p = 0.022), headache (positive: chi-square = 72.5, p = 0.00047) and S-test (positive: chi-square = 97.8, p = 0.00031) as VM; in ear fullness (positive: chi-square = 81.6, p = 0.00064) and ieMRI (positive: chi-square = 149.2, p = 0.00059) as MD, in gender (female: chi-square = 16.4, p = 0.022), evoked dizziness (positive: chi-square = 169.6, p = 0.00030), and SVV (positive: chi-square = 48.4, p = 0.00029) as GPD; and in SDS (high: chi-square = 35.6, p = 0.00088) as Psycho.

To sum up, the ratios of Unknown were significantly reduced by this short-term hospitalization from 244/1905 to 6/240 (chi-square = 22.0, p = 0.00027).

4. Discussion

It is sometimes hard for general otolaryngologists especially at outpatient town clinic to accurately diagnose vertigo/dizziness because of limited time for patients' interview and limited feasible examinations. Generally, 10%-15% of vertigo/dizziness is of unknown origin, regardless of characteristics of facilities [1–5]. Through short-term hospitalization with various vertigo/dizziness examinations, 240 patients with initial vertigo/dizziness of unknown origin were finally diagnosed with BPPV (44.6%), OD (23.3%), VPD (10.4%), VM (5.8%), MD (5.0%), GPD (4.2%), Psycho (4.2%), and Unknown (2.5%). Thus, the ratio of unknow origin could be significantly reduced after this short-term hospitalization. Herein, we have discussed the implications of unknown origin diagnosis and the beneficial effects of an accurate final diagnosis in each disease.

In patients with BPPV, the intensity of vertigo/dizziness and nystagmus is affected by the number of detached otolith and head movement [19, 20]. Therefore, a substantial number of patients with BPPV will not exhibit typical symptoms or findings during examination and testing [2,21]. Factors such as advanced age, the female sex, and an intractable evoked floating sensation should lead us to ask whether BPPV is the cause of vertigo/dizziness. A therapeutic diagnosis of BPPV can be made when positional/positioning nystagmus is repeatedly detected in nystagmus tests and the symptoms are relieved by introducing head elevation sleeping [22,23].

In patients with OD, it is not always possible to measure blood pressure during busy periods at the outpatient care of the Vertigo/Dizziness Center. In addition, many patients do not undergo the S-test, which involves moving from a supine position to standing. Additionally, patients with OD may have a negative S-test depending on their physical condition during the examination. OD tends to occur in young women, however, it should be noted that it is often seen in middle-aged and elderly patients with hypertension who are taking antihypertensive agents. Cerebral anemia, which may occur when the head is kept elevated for a long time, can manifest as an evoked floating sensation that is difficult to cure. When diagnosing OD, it is important not only to measure the blood pressure but also to frequently check fluctuations. As 30% of patients also present with BPPV, it is important to understand whether OD or BPPV is the main pathology involved in the vertigo/dizziness. An autonomic nerve activator is often the first treatment to be considered, but as in patients with BPPV, introducing head elevation sleeping is often effective [24].

With regard to patients with VPD, patients with sudden hearing loss with vestibular neuritis and vertigo/dizziness whose rotatory vertigo persists for several days, are recommended to rest, though motion-evoked vertigo/dizziness may persist afterward. However, such characteristic vertigo/dizziness episodes are rare, which increases the difficulty of diagnosing patients with VPD. Poor vestibular compensation is an after effect of a unilateral or bilateral peripheral vestibular disorder and is suspected to cause an evoked floating sensation that is difficult to cure [25]. Lateral semicircular canal disorders often exhibit abnormalities such as head shaking after nystagmus, however, detecting abnormal nystagmus may be difficult in vertical semicircular canal and otolithic organ disorders. If abnormalities cannot be detected in a simple nystagmus test, a more detailed examination of peripheral vestibular function should be conducted using the C-test, vHIT, and VEMP. The treatment consists of vestibular rehabilitation to promote vestibular compensation [26].

Both patients with VM and MD, involve episodes of rotatory vertigo that last several hours, which may make it relatively easy to suspect the disease. However, if headache symptoms associated with vertigo/dizziness episodes in VM or the cochlear symptoms associated with vertigo/dizziness episodes in MD are vague, and if the patient complains not of rotatory vertigo but of floating sensations, it may be difficult to reach a definitive diagnosis [3]. Along with stronger ques-

tioning about the headaches that accompany vertigo/dizziness episodes in VM, the female sex, a tendency to low blood pressure, and a positive S-test may serve as a reference [27]. As with stronger questioning on the cochlear symptoms that accompany vertigo/dizziness episodes in MD, it may be helpful to reference tests that estimate internal lymphedema, such as contrast-enhanced ieMRI, electrocochleogram, and glycerol testing. Treatment can be performed if these conditions are suspected. A therapeutic diagnosis of VM can be made if anti-migraine agents are effective, and of MD if diuretics are effective [27,28].

The disease concept of GPD was proposed by Wada et al. as a condition involving an issue somewhere in the gravity sensory system from the periphery to the center [29]. Many women who complain of persistent floating sensations without clear nystagmus only exhibit abnormal SVV test results, with all other tests being within the normal ranges. The treatment is vestibular rehabilitation to rectify problems in the gravity sensory system [22,23]. Another possibility is that an acute disturbance of gravity sensitivity due to BPPV or an otolithic organ disorder can manifest as chronic aftereffects in the gravity sensory system. More data needs to be accumulated on this topic.

Psycho is a diagnosis made only if no organic disorder causing vertigo/dizziness is detected and positive responses are given in a neuropsychiatric questionnaire. Persistent postural-perceptual dizziness, which has recently attracted attention as PPPD, is thought to fall under Psycho; however, it can be accompanied by other vertigo and equilibrium disorders. In particular, it is induced by visual stimuli which causes non-specific vertigo/dizziness symptoms [30].

With regard to patients with unknown origin no abnormalities are exhibited in any ontological tests, neuro-ontological tests, imaging tests, autonomic nervous system tests, or questionnaires. While it may include undefined novel forms of vertigo/dizziness, there is a possibility they are due to BPPV or OD that by chance were tested in the remission stage [22,23]. It may further be due to testing in the early stages of a known vertigo/dizziness disorder before abnormal test results appear. Unknown cases should be followed up at regular intervals.

There are at least three limitations of this study. The first is that cVEMP was appropriately performed to check right-left differences to evaluate unilateral otolith dysfunction. However, in our facility, bilateral otolith disorder may not be picked up by quantitative values of cVEMP. The second is that PPPD was not focused as diagnostic category in the present study, since PPPD is diagnosed mainly by subjective findings and easily overlapped with other vertigo/dizziness diseases [30]. We would like to discuss the diagnostic issues of chronic vertigo/dizziness together with PPPD in the later communication. The third is that the diagnosis of chronic vertigo/dizziness depends on how close to the target patients' interview is to their past history and how detailed the outpatient clinic's facility for examinations are. This means that there is a large variety by the quality of diagnostic ability for chronic vertigo/dizziness in outpatient clinic. We did not understand all these clinics around our university hospital. However, it could be said that careful patients' interview and feasible otology/neurotology examinations significantly reduce the ratios of Unknown.

Of course, most physicians especially with vertigo/dizziness specialty can diagnose patients accurately according to the diagnostic guideline of the ICVD [6–10]. We believe that this study may provide helpful information of disease statistics among patients defined as Unknown, when patients' past history and/or a clinical exam facility are inadequate. Thus, using this helpful information, general otolaryngologists at outpatient town clinic may determine whether to treat their patients through therapeutic diagnosis or refer them to another hospital for extensive otology/neurotology exams.

5. Conclusion

General otolaryngologists at outpatient town clinic have a tendency to make diagnosis as Unknown easily due to limited time to interview with their patients under inadequate exam facilities. Accurate diagnosis is essential for doctors to select an appropriate therapeutic strategy to promptly cure a disease. Otology/neurotology examinations, inner ear MRI, and scoring questionnaires may contribute to the accurate diagnosis of vertigo/dizziness patients with unknown origin. Answering lists (i.e. disease statistics) for vertigo/dizziness of unknown origin obtained in the present study may be helpful for these general otolaryngologists to access the accurate final diagnosis.

Declaration of Competing Interest

The present study does not include any conflicts of interest.

Acknowledgments

The authors wish to thank Dr. Masashi Choubi, a registered statistician (certificate number: 622017), for the helpful advice on the statistical analyses. This study was supported in part by JSPS KAKENHI Grant (2020-2022), AMED under Grant Number 18dk0310092h000a and the Health and Labour Sciences Research Grant for Research on Rare and Intractable Diseases (R02-Nanchito (Nan)-Ippan-004) from the Ministry of Health, Labour, and Welfare of Japan.

References

[1] Friedland DR, Tarima S, Erbe C, Miles A. Development of a statistical model for the prediction of common vestibular diagnoses. JAMA Otolaryngol Head Neck Surg 2016;142:351–6.

[2] Kitahara T, Ota I, Horinaka A, Ohyama H, Sakagami M, Ito T, et al. Idiopathic benign paroxysmal positional vertigo with persistent vertigo/dizziness sensation is associated with latent canal paresis, endolymphatic hydrops and osteoporosis. Auris Nasus Larynx 2019;46:27–33.

[3] Kitahara T, Sakagami M, Ito T, Shiozaki T, Kitano K, Yamashita A, et al. Meniere's disease with unremitting floating sensation is associated with canal paresis, gravity sensitive dysfunction, mental illness, and bilaterally. Auris Nasus Larynx 2019;46:186–92.

[4] Ozono Y, Kitahara T, Tomiyama Y, Nishiike S, Morita H, Inohara H. Differential diagnosis of vertigo and dizziness at the emergency department. Acta Otolaryngol 2014;134:140–5.

[5] Neuhauser HK. The epidemiology of dizziness and vertigo. Handb Clin Neurol 2016;137:67–82.
[6] von Brevern M, Bertholon P, Brandt T, Fife T, Imai T, Nuti D, et al. Benign paroxysmal positional vertigo: diagnostic criteria. J Vestib Res 2015;25:105–17.
[7] Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Meniere's disease. J Vestib Res 2015;25:1–7.
[8] Strupp M, Zingler VC, Arbusow V. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. N Engl J Med 2004;351:354–61.
[9] Strupp M, Kim JS, Murofushi T, Straumann D, Jen JC, Rosengren SM, et al. Bilateral vestibulopathy: diagnostic criteria consensus document of the classification committee of the Barany society. J Vestib Res 2017;27:177–89.
[10] Lempart T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, et al. Vestibular migraine: diagnostic criteria. J Vestib Res 2012;22:167–72.
[11] Inoue H, Uchi Y, Nogami K, Uemura T. Low-dose intratympanic gentamicin treatment of Meniere's disease. Eur Arch Otorhinolaryngol 1994;251:12–14.
[12] Aoki S, Arai Y, Ide N, Sugiura E, Miyajima K, Tanaka N. Clinical significance of vertical component of caloric response including its second phase in vertiginous patients. Acta Otolaryngol 2007;127:1142–9.
[13] McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The Video Head Impulse Test (vHIT) of semicircular canal function–age-dependent normative values of VOR gain in healthy subjects. Front Neurol 2015;6:154.
[14] Papathanasiou ES, Murofushi T, Akin FW, Colebatch JG. International guidelines for the clinical application of cervical vestibular evoked myogenic potentials: an expert consensus report. Clin Neurophysiol 2014;125:658–66.
[15] Sun DQ, Zuniga MG, Davalos-Bichara M, Carey JP, Agrawal Y. Evaluation of a bedside test of utricular function - the bucket test. Acta Otolaryngol 2014;134:382–9.
[16] Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid after intravenous administration of single-dose gadodiamide. Magh reson Med Sci 2012;11:145–50.
[17] Nakashima T, Naganawa S, Pyykko I, Gibson WP, Sone M, Nakata S, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol Suppl 2009;129:5–8.
[18] Fukuda K, Kobayashi S. A study on a self-rating depression scale. Seishin Shinkeigaku Zasshi 1973;75:673–9.
[19] Schuknecht HF. Cupulolithiasis. Arch Otolaryngol 1969;90:113–26.
[20] Hall SF, Ruby PRF, McClure JA. The mechanics of benign paroxysmal positional vertigo. J Otolaryngol 1979;8:151–8.
[21] House MA, Honrubia V. Theoretical models for the mechanisms of benign paroxysmal positional vertigo. Audiol Neurotol 2003;8:91.
[22] Horinaka A, Kitahara T, Shiozaki T, Ito T, Wada Y, Yamanaka T, et al. Head-up sleep may cure patients with intractable benign paroxysmal positional vertigo: a six-month randomized trial. Laryngoscope Investig. Otolaryngol 2019;4:353–8.
[23] Kitahara T, Horinaka A, Shiozaki T, Ito T, Yamanaka T, Nario K. Combination of head-up sleep and vertical recognition training may cure intractable motion-evoked dizziness with unknown origin. Acta Otolaryngol 2020 in press.
[24] Cooper VL, Hainsworth R. Head-up sleeping improves orthostatic tolerance in patients with syncope. Clin Auton Res 2008;18:318–24.
[25] Kitahara T, Takeda N, Nishiike S, Okumura S-I, Kubo T. Prognosis of inner ear periphery and central vestibular plasticity in sudden deafness with vertigo. Ann Otol Rhinol Laryngol 2005;114:786–91.
[26] Hillier S, McDonnell M. Is vestibular rehabilitation effective in improving dizziness and function after unilateral peripheral vestibular hypofunction? An abridged version of a Cochrane review. Eur J Phys Rehab Med 2016;52:541–56.
[27] Byun YJ, Levy DA, Nguyen SA, Brennan E, Rizk HG. Treatment of vestibular migraine: a systematic review and meta-analysis. Laryngoscope 2020 in press.
[28] Claes J, Van de Heyning PH. A review of medical treatment for Meniere's disease. Acta Otolaryngologica Suppl 2000;544:34–9.
[29] Wada Y, Yamanaka T, Kitahara T, Kurata J. Effect of head roll-tilt on the subjective visual vertical in healthy participants: Towards better clinical measurement of gravity perception. Laryngoscope Investig Otolaryngol 2020;5 (In press). doi:10.1002/lio2.461.
[30] Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T, et al. Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the classification of vestibular disorders of the Barany society. J Vestib Res 2017;27:191–208.