Effects of Kampo medicine hangebyakujutsutemmato on persistent postural-perceptual dizziness: A retrospective pilot study

Toru Miwa, Shin-ichi Kanemaru

BACKGROUND
Persistent postural-perceptual dizziness (PPPD) is a functional disorder, typically preceded by acute vestibular disorders. It is characterized by a shift in processing spatial orientation information, to favor visual over vestibular and somatosensory inputs, and a failure of higher cortical mechanisms. To date, no therapies for PPPD have been approved. Kampo medicine hangebyakujutsutemmato (HBT) has been reported to alleviate disturbances of equilibrium. We hypothesized that HBT would be a beneficial treatment for PPPD.

AIM
To examine the efficacy of HBT for the treatment of PPPD.

METHODS
Patients with PPPD were enrolled and divided into two groups: The HBT group (n = 24) and the non-HBT group (n = 14). The participants completed questionnaire surveys [Niigata PPPD questionnaire (NPQ), dizziness handicap inventory, hospital anxiety and depression scale (HADS), orthostatic dysregulation questionnaire, pittsburg sleep quality index (PSQI), and motion sickness scores] before and after HBT treatment. Additionally, to identify HBT responders, multivariate regression analysis was performed using the results of the questionnaire surveys and equilibrium tests; including stabilometry, and caloric, vestibular evoked myogenic response, and head-up tilt tests.

RESULTS
Thirty-eight outpatients were included in this study, of which 14 patients (3 men, 11 women; mean age, 63.5 ± 15.9 years) received treatment without HBT, and 24 (1 man, 23 women; mean age, 58.2 ± 18.7 years) received combination treatment with HBT. Following HBT treatment, NPQ scores decreased significantly (baseline 40.1 ± 10.0 vs 2 mo 24.6 ± 17.7, P < 0.001). No statistically significant changes were observed in the NPQ scores in the non-HBT group (baseline 38.6 ± 12.2 vs 2 mo 39.4 ± 14.4, P = 0.92). Multivariable regression analysis revealed that the results of stabilometry (P = 0.02) and the caloric (P = 0.03), and head-up tilt tests (P < 0.001), HADS (P = 0.003), and PSQI (P = 0.01) were associated with HBT responsiveness in PPPD patients.

CONCLUSION

HBT may be an effective adjunct therapy for PPPD. Patients with autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality may be high responders to HBT.

Key Words: Hangebyakujutsutemmato; Kampo medicine; Persistent postural-perceptual dizziness; Niigata persistent postural-perceptual dizziness questionnaire score; Sensory reweighting; Treatment responder

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Persistent postural-perceptual dizziness (PPPD) is characterized by a shift in processing spatial orientation information to favor visual or somatosensory information over vestibular inputs, as well as failure of higher cortical mechanisms. Our retrospective study showed that Kampo medicine Hangebyakujutsutemmato (HBT) was effective as an adjunctive therapy for PPPD. Additionally, HBT responders had baseline autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality. According to our results, and previous reports, several herbal ingredients in HBT might improve autonomic function and the cyclic AMP response element binding protein/brain-derived neurotrophic factor pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

Citation: Miwa T, Kanemaru S. Effects of Kampo medicine hangebyakujutsutemmato on persistent postural-perceptual dizziness: A retrospective pilot study. World J Clin Cases 2022; 10(20): 6811-6824

URL: https://www.wjgnet.com/2307-8960/full/v10/i20/6811.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i20.6811

INTRODUCTION

Persistent postural-perceptual dizziness (PPPD) is a novel disorder characterized by functional dizziness, but it is neither a structural nor a psychiatric condition. PPPD supersedes phobic postural vertigo (PPV) and chronic subjective dizziness (CSD) and is characterized by a persistent chronic vestibular syndrome lasting > 3 mo that is typically preceded by acute vestibular disorders[1]. The core vestibular symptoms of PPPD are dizziness, unsteadiness, or non-spinning vertigo, which are exacerbated by an upright posture/walking, active or passive movement, and exposure to movement or complex visual stimuli[1]. The presence of three exacerbating factors is a characteristic of PPPD[1]. No specific laboratory test for PPPD is available, and the precise assessment of symptoms, exacerbating factors, and medical history is important for diagnosis[1]. The disorder constitutes a long-term maladaptation to a neuro-otological, medical, or psychological event that triggers vestibular symptoms and is usually considered within the spectrum of other functional neurological disorders. Studies of PPV and CSD suggest that the long-term benefit of therapy likely depends on early initiation of treatment[2]. Years of chronicity usually suggest a higher degree of maladaptation, more severe disability, and more engrained illness beliefs. Despite efforts to unify the diagnosis of functional (somatoform) dizziness, patients present with a variety of triggers, perpetuating factors, and comorbidities, thus requiring individualized treatment. To date, no potential therapies for PPPD have been evaluated in randomized controlled clinical trials or been approved as a cure for this condition. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)[3,4], vestibular rehabilitation (VR)[4,5], cognitive-behavioral therapy (CBT)[6-9] and electrical stimulation[10] have been investigated as potential treatments for PPPD.

The Japanese herbal medicine hangebyakujutsutemmato (HBT; Kraacie Co., Tokyo, Japan) has been used to prevent Meniere’s disease, dizziness, nausea, hypotension, headache, and stomach disorders by eliminating excess water from the body[11-14]; in traditional Chinese herbal medicine, fluid retention is
attributable to the presence of unbalanced and mal-distributed water in the body.[13] HBT is composed of 12 crude herbal extracts which improve digestion to assist in the removal of excess fluid.[15] Regarding its potential as a therapy for PPPD, HBT has been reported as a potential treatment for CSD [13,16,17]. In addition, some reports indicated that HBT was effective in preventing dizziness caused by opioids[18] or pregabalin[19]. Thus, HBT is a promising drug based on its demonstrated effects on dizziness.

Our aim was to examine the efficacy of HBT for PPPD. We hypothesized that HBT could be an efficacious treatment for PPPD. In addition, we hypothesized that autonomic function disturbances could contribute to HBT responsiveness in patients with PPPD.

**MATERIALS AND METHODS**

**Participants**

Data, including sex, age, symptoms, and diagnosis, which were obtained on the day of ENT consultation, between January 1, 2020 and December 31, 2020, were collected from hospital medical records and analyzed. Patient inclusion criteria were as follows: (1) Age 20 to 100 years; (2) A score of more than 27 points on the Niigata PPPD questionnaire (NPQ, a 12-item questionnaire that evaluates the three exacerbating factors for PPPD[20]) after treatment with combined general non-Kampo drugs for vertigo/dizziness for more than 3 mo; and (3) Visited our hospital more than three times between January 1, 2020 and December 31, 2020. The exclusion criteria were as follows: (1) Treatment with a Kampo medicine other than HBT; (2) Asthma or significant uncontrolled cardiac, pulmonary, gastrointestinal, renal, hepatic, endocrine, musculoskeletal, or oncological disorder or comorbidity that would likely prevent completion of the study; and (3) Less than two visits to our hospital. The clinical diagnosis of balance disorders was based on the diagnostic criteria published by the Japan Society for Equilibrium Research[21,22] and the Barany Society[1].

**Primary and secondary endpoint measures and outcomes**

This was a retrospective chart review. Patients were administered HBT extract (7.5 g/day) (Kracie Co., Tokyo, Japan; HBT group) or not (non-HBT group) for 3 mo. HBT was administered orally, twice daily, before eating. The quality of the HBT was standardized based on the Good Manufacturing Practices defined by the Ministry of Health, Labour and Welfare of Japan, and the quality of KB-37 was evaluated by 3D-HPLC analysis performed elsewhere. All patients took medications (non-Kampo) other than HBT for the treatment of vertigo/dizziness. We did not limit the use of other medications. In addition, all patients underwent VR for vestibular compensation, via the vestibulo-ocular reflex, three times at home.

Assessments were performed at baseline and every month after the start of the study. All participants completed clinical questionnaire-based surveys regarding balance disorders at each visit to our hospital (at least three times). The clinical surveys administered included the NPQ[20], dizziness handicap inventory (DHI)[23,24], hospital anxiety and depression scale (HADS)[25,26], orthostatic dysregulation (OD) Questionnaire[27,28], Graybiel’s Motion Sickness Score[29], and Pittsburgh sleep quality index (PSQI)[30,31]. All participants underwent equilibrium testing at the first visit to our hospital. The equilibrium tests included static stabilometry, with or without foam posturography, to assess steady-state postural control and to detect visual and somatosensory dependence in patients[32]; the foliage test (FT), a stepping test on a force platform, to assess dynamic postural control[33-36]; the cervical vestibular-evoked myogenic potential (cVEMP) test to assess the function of the saccule-inferior vestibular nerve system[37]; ocular VEMP (oVEMP) testing to assess the function of the utricle-superior vestibular nerve system[38]; caloric testing to assess the function of the lateral semicircular canal-utricle-superior vestibular nerve system[39]; head-up tilt (HUT) testing to assess OD, which is related to autonomic dysfunction[40]; and nystagmus testing to assess vestibular function.

The methodological details and criteria for the questionnaires and tests are described in Supplementary Table 1. During stabilometry, the patients stood on a strain-gauge force platform (GP-5000 stabilometer; Anima, Tokyo, Japan) for 60 s with their eyes open with and without the foam rubber, and with their eyes closed with and without the foam rubber[41]. The measurements were performed under background noise conditions (approximately 50 dB). Somatosensory weighting was assessed by six parameters: The velocity and area of movement of the center of pressure with eyes closed/foam rubber (velocity, VCF; area, ACF) to assess vestibular weighting, the Romberg ratio of velocity and area with foam rubber (velocity; area-ARF) to assess visual weighting, and foam ratios (ratios of a measured parameter with to without the foam rubber) of velocity and area with eyes closed (velocity-VFCF and area-AFCF)[41]. The FT is a quantified stepping test performed at a set tempo of 120 bpm while standing upright with the arms placed at the side of the body, in a closed foot position, with the toes continuously touching the plate, so that the participant can change only the height of the heels to rise in alternation[33,42-44]. The parameters of the FT include the FT value (area of the front-back width of the locus) with eyes open and closed and the dynamic Romberg ratio (FT value of close/open eyes)[33,42-44]. During the cVEMP test, the patient’s neck was rotated to the left as far as possible (approximately 70-80 degrees). The stimulation used clicks with a 120 dB sound pressure level lasting
Table 1 Patients’ demographic information (mean ± SD)

|                      | Non-HBT (n = 14) | HBT (n = 24) | P value |
|----------------------|------------------|--------------|---------|
| Age (yr)             | 63.5 ± 15.9      | 58.2 ± 18.7  | 0.19a   |
| Sex (Male:Female)    | 3:11             | 1.23         | 0.21b   |
| Vestibular disease   | Meniere’s disease; 12; BPPV: 2 | Meniere’s disease; 23; BPPV: 1 | 0.23c   |

a Unpaired t-test.
b Fisher’s exact test.
HBT: Hangebyakujutemmato; SD: Standard deviation; BPPV: Benign paroxysmal positional vertigo.

0.1 ms, with a stimulation frequency of 5 Hz and an analysis time of 50 ms. The electromyographic responses to 200 stimuli were averaged and recorded using an evoked potential recorder with a band-pass filter of 20–2000 Hz (Neuropack; Nihon Kohden, Tokyo, Japan). To assess cVEMP amplitude, the asymmetry ratio (AR) was used, which was defined as the difference between the large amplitude (AL) and small amplitude (AS) of peak 13 to peak n23 divided by the sum of both amplitudes presented as a percentage, that is, |(AL - AS)/(AL + AS)| × 100 (%). The normal range of AR was defined as less than 33%[45]. During the oVEMP test, the patient maintained an upward gaze at 30° with the electrodes on the face just inferior to each eye. Stimulation included 0.1 ms clicks and 500 Hz short tone bursts (Neuropack). To assess oVEMP amplitude, AR was performed in a manner similar to cVEMP. The normal AR range was defined as less than 33%[46]. During the caloric test, stimulation was provided through sequential irrigation of each ear with 5 mL of water for 10 s. The maximum slow-phase velocity was measured using videonystagmography recordings (ENG, Nagashima, Tokyo, Japan). Canal paresis % (CP%) was calculated as described previously[47]. The CP% normal range was defined as less than 20%[48]. The HUT test was performed according to the method established by the Japan Society of Neurovegetative Research in 2015[49]. Non-invasive oscillatory measurements of blood pressure (BP), pulse rate, coefficient of variation of the R-R interval (CVRR), parasympathetic nerve function [high-frequency component (HF)], and sympathetic nerve function [low-frequency component (LF)/HF] were performed three times using an automated sphygmomanometer (Meijin + Circlemates; Crosswell, Tokyo, Japan) at the following time points: (1) After 5 min in the supine position; (2) After 1 min of standing; and (3) After 10 min of standing. The cuff of the BP-recording device was attached to the left arm, which was supported at the heart level throughout the study. The testing was conducted during the daytime, in a quiet environment, at a constant room temperature of 22 °C–25 °C to exclude the effects of chronobiologic factors on the outcomes of the test. The participants maintained a regular meal schedule but were restricted from smoking and caffeine ingestion for 6 h before the examination. The intake of foods and medications with sympathomimetic activity was also prohibited before the study. The results were determined as positive or negative according to the outcome of the HUT test and the international scientific definition of OD (Supplementary Table 1)[40]. Regarding systolic BP, diastolic BP, heart rate, CVRR, HF, and LF/HF, the change ratio was calculated as a measured parameter of (2)/(1) for the immediate change ratio and (3)/(2) for the delayed change ratio. Nystagmus was evaluated using an infrared charge-coupled device camera. When pathologic nystagmus (i.e., spontaneous nystagmus or positional nystagmus) was observed, the test result was considered positive.

The primary outcome was the therapeutic effect on PPPD and the secondary outcome was autonomic dysfunction for the prediction of benefit.

Statistical analyses

Power and sample size calculations were conducted before and after data collection using PS software (Ver. 3.1.6, Vanderbilt University, Nashville, TN)[50]. The statistical review of the study was performed by a biomedical statistician. For non-parametric analysis of subjective variables which were not normally distributed, the Wilcoxon signed-rank test was used to investigate changes in the questionnaire scores. For parametric analysis of subjective variables which were normally distributed, unpaired t-tests were used to investigate age variables. Fisher’s exact test was used to compare sex and vestibular disease variables with a non-normal distribution. Regarding the primary outcome, changes in NPQ scores were compared using a one-way analysis of variance and post-hoc Tukey test, and NPQ scores between groups were compared using the Kruskal–Wallis test and the post-hoc two-stage linear step-up procedure; this was done to avoid an inflated Type I error rate because the data were normally distributed. NPQ score improvements were compared using a mixed-effect analysis and post-hoc Bonferroni’s multiple comparison test because of the number of missing values. Residual plots were used to confirm the correctness of the assumptions made for both primary outcomes. Regarding secondary outcomes, multivariate regression analysis was performed to identify HBT responders. Questionnaire survey data and equilibrium test results at the first visit to our hospital were used for the HBT group. The outcome variable was the rate of improvement in total NPQ scores after 2 mo of HBT treatment. Due to the small number of participants, multivariate regression analysis was performed to
divide the explanatory variables into equilibrium tests, HUT results, and questionnaire survey results. The model was created after confirming the variance inflation factor. The explanatory variances were selected according to the Akaike information criterion. Missing values were imputed using the RF method. There were no outliers in the analysis of either primary or secondary outcomes. Statistical significance was set at $P < 0.05$. Evaluations were determined as ‘not applicable’ if the calculated sample size after data collection was insufficient for statistical analysis. All statistical analyses were performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California United States, www.graphpad.com).

RESULTS

Patient information
Thirty-eight outpatients were included in this study. A total of 14 patients (three men, 11 women; mean ± SD, 63.5 ± 15.9 years) received treatment without HBT (non-HBT group) and 24 patients (one man, 23 women; mean age, 58.2 ± 18.7 years) received combination treatment with HBT (HBT group). Table 1 shows the clinical characteristics of the participants in the non-HBT and HBT groups. Characteristics such as sex, age, and vestibular disease were not significantly different between the two groups (Table 1, age, $P = 0.19$; sex, $P = 0.21$; vestibular disease, $P = 0.25$).

NPQ scores improved in the HBT group
No statistically significant changes in NPQ scores were observed in the non-HBT group (Figure 1A: Baseline vs 1 mo, $P = 0.98$; 1 mo vs 2 mo, $P = 0.94$; baseline vs 2 mo, $P = 0.92$). In the HBT group, NPQ scores showed a statistically significant increase (Figure 1B: Baseline vs 1 mo, $P = 0.002$; 1 mo vs 2 mo, $P = 0.003$; baseline vs 2 mo, $P < 0.001$). In the non-HBT group, there was no significant difference in the NPQ subcategory scores for upright posture/walking (Figure 2A: Baseline vs 1 mo, $P = 0.67$; 1 mo vs 2 mo, $P = 0.73$; baseline vs 2 mo, $P = 0.41$) or movement (Figure 2B: Baseline vs 1 mo, $P = 0.50$; 1 mo vs 2 mo, $P > 0.99$; baseline vs 2 mo, $P = 0.38$), while the score for visual stimulation showed a significant difference at month 2 (Figure 2C: Baseline vs 1 mo, $P = 0.11$; 1 mo vs 2 mo, $P = 0.53$; baseline vs 2 mo, $P = 0.02$). In the HBT group, NPQ subcategory scores showed statistically significant differences for upright posture/walking (Figure 2D: Baseline vs 1 mo, $P = 0.04$; 1 mo vs 2 mo, $P = 0.005$; baseline vs 2 mo, $P < 0.001$) and visual stimulation (Figure 2F: Baseline vs 1 mo, $P = 0.002$; 1 mo vs 2 mo, $P = 0.03$; baseline vs 2 mo, $P < 0.001$), and visual stimulation showed no significant differences (Figure 3F: Baseline, $P = 0.11$; 1 mo, $P > 0.99$; 2 mo, $P = 0.06$).
A-C: There was no significant difference in the Niigata persistent postural-perceptual dizziness questionnaire (NPQ) subcategory scores in the non-hangebyakujutsutemmato (HBT) group except for the NPQ visual subcategory: A: Upright posture/walking: Baseline vs 1 mo, \( P = 0.67; \) 1 mo vs 2 mo, \( P = 0.73; \) baseline vs 2 mo, \( P = 0.41; \) B: Movement: Baseline vs 1 mo, \( P = 0.50; \) 1 mo vs 2 mo, \( P > 0.99; \) baseline vs 2 mo, \( P = 0.38; \) C: Visual stimulation: Baseline vs 1 mo, \( P = 0.11; \) 1 mo vs 2 mo, \( P = 0.53; \) baseline vs 2 mo, \( P = 0.02; \) D-F: In the HBT group, NPQ subcategory scores showed statistically significant differences: D: Upright posture/walking: Baseline vs 1 mo, \( P = 0.04; \) 1 mo vs 2 mo, \( P = 0.005; \) baseline vs 2 mo, \( P < 0.001; \) E: Movement: Baseline vs 1 mo, \( P = 0.01; \) 1 mo vs 2 mo, \( P = 0.006; \) baseline vs 2 mo, \( P < 0.001; \) F: Visual stimulation, baseline vs 1 mo, \( P = 0.002; \) 1 mo vs 2 mo, \( P = 0.03; \) baseline vs 2 mo, \( P < 0.001; \).

Other factors were not influenced by HBT treatment in PPPD patients

To examine the effect of HBT on other factors, we compared the questionnaire survey results at baseline, 1 mo, and 2 mo. No statistically significant differences in the DHI, including subcategories; HADS, including subcategories; OD scores; Graybiel’s motion sickness scores; or PSQI at baseline, were observed between the two groups (Table 2).

**HBT responders had autonomic dysfunction, unstable balance, CP, anxiety, and poor sleep quality at baseline**

To identify HBT responders among PPPD patients, we performed multivariate regression analysis. We identified the rate of improvement in NPQ scores. ACF, ARF, VFVF, AFCF in static stabilometry, CP% of the caloric test, and the existence of OD at the first visit to our hospital were significant factors for HBT responsiveness (Table 3: ACF, \( P = 0.02; \) ARF, \( P = 0.01; \) VFVF, \( P = 0.03; \) AFCF, \( P = 0.03; \) CP%, \( P = 0.03; \) OD, \( P < 0.001\)). To investigate the precise influence of OD on HBT responders, we performed multivariate regression analysis using the explanatory variables of the HUT test. The results showed that the immediate change ratio of HR and CVRR and delayed change ratio of HF and LF/HF were significant factors for HBT responsiveness in PPPD patients (Table 4: Immediate change ratio of HR, \( P = 0.009; \) immediate change ratio of CVRR, \( P = 0.03; \) delayed change ratio of HF, \( P = 0.006; \) delayed change ratio of LF/HF, \( P = 0.04). \) In addition, regarding the questionnaire surveys, dizziness handicap index–emotional (DHI-E), HADS-anxiety (HADS-A), and PSQI were significant factors for HBT responsiveness (Table 5: DHI-E, \( P = 0.01; \) HADS-A, \( P = 0.003; \) PSQI, \( P = 0.01)\).

**DISCUSSION**

PPPD is a newly defined diagnostic syndrome that unifies the key features of PPV, CSD, and related disorders[1]. Although the exact pathophysiology of PPPD remains to be elucidated, data from...
Table 2 Other factors influenced by hangebyakujutsutemmato treatment in Persistent postural-perceptual dizziness patients

| Subcategory | Non-HBT (n = 14) | HBT (n = 24) | P value¹ |
|-------------|-----------------|-------------|---------|
| DHI         | Baseline        | 49.6 ± 24.6 | 50.8 ± 20.1 | 0.44 |
|             | 1 mo            | 45.7 ± 25.8 | 43.0 ± 3.0  | 0.37 |
|             | 2 mo            | 42.7 ± 25.0 | 38.8 ± 24.3 | 0.32 |
| DHI-P       | Baseline        | 11.9 ± 7.6  | 14.9 ± 6.2  | 0.11 |
|             | 1 mo            | 11.4 ± 7.1  | 11.8 ± 7.1  | 0.43 |
|             | 2 mo            | 11.0 ± 6.8  | 11.3 ± 6.9  | 0.46 |
| DHI-E       | Baseline        | 19.6 ± 8.9  | 16.7 ± 8.6  | 0.17 |
|             | 1 mo            | 17.3 ± 9.7  | 14.7 ± 9.0  | 0.21 |
|             | 2 mo            | 15.3 ± 9.5  | 12.7 ± 9.7  | 0.21 |
| DHI-F       | Baseline        | 18.1 ± 11.3 | 19.3 ± 8.8  | 0.38 |
|             | 1 mo            | 17.0 ± 11.8 | 16.5 ± 10.1 | 0.45 |
|             | 2 mo            | 16.4 ± 10.6 | 14.8 ± 9.7  | 0.32 |
| HADS        | Baseline        | 15.8 ± 8.3  | 15.0 ± 7.3  | 0.39 |
|             | 1 mo            | 15.6 ± 7.8  | 13.8 ± 8.6  | 0.25 |
|             | 2 mo            | 15.6 ± 8.6  | 13.0 ± 9.5  | 0.19 |
| HADS-A      | Baseline        | 8.9 ± 5.0   | 9.0 ± 4.0   | 0.49 |
|             | 1 mo            | 8.1 ± 4.4   | 7.8 ± 4.4   | 0.42 |
|             | 2 mo            | 7.9 ± 5.0   | 7.7 ± 4.8   | 0.45 |
| HADS-D      | Baseline        | 6.9 ± 4.1   | 6.1 ± 4.3   | 0.29 |
|             | 1 mo            | 7.6 ± 4.5   | 6.0 ± 4.7   | 0.16 |
|             | 2 mo            | 7.7 ± 4.8   | 5.3 ± 5.3   | 0.08 |
| OD score    | Baseline        | 6.1 ± 2.2   | 7.8 ± 5.4   | 0.08 |
|             | 1 mo            | 5.9 ± 2.6   | 5.9 ± 2.9   | 0.48 |
|             | 2 mo            | 5.6 ± 3.0   | 5.6 ± 2.6   | 0.48 |
| Graybiel’s motion sickness score | Baseline | 26.0 ± 11.0 | 25.8 ± 11.2 | 0.47 |
|             | 1 mo            | 19.3 ± 7.6  | 19.9 ± 8.4  | 0.41 |
|             | 2 mo            | 23.3 ± 12.4 | 18.1 ± 6.9  | 0.08 |
| PSQI        | Baseline        | 8.9 ± 3.5   | 10.0 ± 3.4  | 0.19 |
|             | 1 mo            | 8.6 ± 3.0   | 9.0 ± 4.6   | 0.37 |
|             | 2 mo            | 8.5 ± 3.1   | 9.6 ± 4.1   | 0.19 |

¹Wilcoxon signed-rank test.

To examine the effects of HBT on other factors, we compared the questionnaire survey at baseline, 1 mo, and 2 mo. No statistically significant differences in the DHI including subcategories, HADS including subcategories, OD scores, Graybiel’s motion sickness scores, or PSQI at baseline were observed between the two groups. HBT: Hangebyakujutsutemmato; DHI: Dizziness handicap inventory; HADS: Hospital anxiety and depression scale; HADS-A: Hospital anxiety and depression scale–anxiety; HADS-D: Hospital anxiety and depression scale–depression subscale; OD: Orthostatic dysregulation; PSQI: Pittsburgh sleep quality index.

Physiological investigations and rapidly emerging advanced structural and functional neuroimaging studies of patients with PPV, CSD, and PPPD have revealed three key mechanisms by which this disorder is thought to develop: Stiffened posture, a shift in processing spatial orientation information to favor visual over vestibular inputs, and failure of higher cortical mechanisms to modulate the first two processes[51,52]. Maladaptive cognitive-behavioral responses commonly add secondary psychological and functional morbidity, such as fear of falling, anxiety or depressive disorders, and functional gait abnormalities[53,54].
Table 3 Equilibrium test factors related to Nilgata persistent postural-perceptual dizziness questionnaires improvement at 2 mo

|                      | Estimate | SE   | t value | P value |
|----------------------|----------|------|---------|---------|
| (Intercept)          | -0.18    | 0.31 | -0.58   | 0.571   |
| Static stabilometry  |          |      |         |         |
| ACF                  | -0.01    | 0.005| -2.53   | 0.02*   |
| VRF                  | -0.30    | 0.19 | -1.55   | 0.14    |
| ARF                  | 0.33     | 0.11 | 2.99    | 0.01*   |
| VFCF                 | 0.33     | 0.14 | 2.29    | 0.03*   |
| AFCF                 | -0.09    | 0.04 | -2.34   | 0.03*   |
| Dynamic stabilometry |          |      |         |         |
| FT value in closed eye | -0.03    | 0.02 | -1.29   | 0.21    |
| Vestibular function  |          |      |         |         |
| CP (%) of caloric test | 0.004    | 0.002| 2.28    | 0.03*   |
| AR (%) of cVEMP      | 0.005    | 0.003| 1.46    | 0.16    |
| AR (%) of oVEMP      | -0.008   | 0.005| -1.47   | 0.16    |
| Autonomic function   |          |      |         |         |
| OD                   | 0.77     | 0.11 | 6.65    | < 0.001b|

*P < 0.05.

VCF: Center of pressure velocity in the eyes closed/foam rubber condition; ACF: Envelopment area tracing by movement of the center of pressure in the eyes closed/foam rubber condition; VRF: Romberg’s ratio of velocity with foam rubber; ARF: Romberg’s ratio of area with foam rubber; VFCF: Foam ratio of velocity in the eyes closed/foam rubber condition; FT value: Foulage test value; CP (%): Canal paresis in caloric test; AR (%): Asymmetry ratio; cVEMP: Cervical vestibular evoked myogenic responses; oVEMP: Ocular vestibular-evoked myogenic responses; OD: Orthostatic dysregulation. Residual standard error = 0.20 (df = 13; multiple R-squared = 0.81; adjusted R-squared = 0.67, F-statistic = 5.77 (df = 10 and 13; P value = 0.002, Akaike information criterion = -68.7).

Therefore, strategies for the treatment of PPPD are as follows: strategy 1, therapy for comorbidities including vestibular diseases; strategy 2, sensory reweighting of posture; and strategy 3, increased tolerance of a perceived stimulus via desensitizing. SSRIs and SNRIs act on serotonergic pathways in the CNS[3,55] and thus address strategies 1 and 2. Since rehabilitation from PPPD relies on “re-adaptation” of the vestibular and balance systems, vestibular suppressant drugs such as antihistamines and benzodiazepines can be expected to delay rather than hasten rehabilitation and should be avoided if possible[56]. VR is an umbrella term for a range of physical treatments that aim to compensate or restore impaired balance in various vestibular and neurological disorders. For example, PPPD patients often exhibit hyper-visual sensation, which VR aims to desensitize using habituation exercises and relaxation techniques[5,6]. As such, VR may address strategies 2 and 3. CBT was responsible for guiding self-observation on physical, emotional, and psychosocial levels to break out of maladaptive cognitive-behavioral cycles. Desensitizing exercises can be used to increase the tolerance of perceived disequilibrium and reduce automatic “high-risk” postural strategies[7,8]. Thus, CBT may address strategy 3. The present results showed that NPQ scores improved significantly in patients treated with HBT compared with those not treated with HBT. Notably, the visual score in the HBT group showed significantly greater improvement compared with the non-HBT group.

HBT is a powdered extract obtained by spray drying a hot water extract mixture of the following 12 crude herbal drug extracts: Citrus unshiu peel (1.0 g, 12%), Pinellia tuber (1.0 g, 12%), Atractylodes rhizome (1.0 g, 12%), Atractylodes Lancea Rhizome (1.0 g, 12%), Poria sclerotium (1.0 g, 12%), gastrodia tuber (0.75 g, 8%), malt (0.75 g, 8%), Astragalus root (0.5 g, 6%), Alisma Tuber (0.5 g, 6%), ginseng (0.5 g, 6%), Phellodendron bark (0.325 g, 4%), and ginger (0.1625 g, 2%). Supplementary Figure 1 shows the components and effects of HBT. HBT was shown to alleviate inner ear immune injury in a rat model[19] and disturbance of equilibrium resulting from pregabalin in a rat model of neuropathic pain[19]. The components of HBT have various pharmacological effects on vertigo/dizziness/vomit/nausea. Alkaloids in Pinellia Tuber, Atractylenolide III in Atractylodes rhizome, and 6-shogaol in ginger affect gastroesophageal vagal nodose C-fibers to relieve nausea/vomiting and gastrointestinal discomfort[57-59] when vertigo/dizziness occurs. Atractylenolide III in Atractylodes rhizome, triterpenes, and polysaccharides in Poria sclerotium, and triterpenoids in Alisma Tuber have antiduressive effects[13,15,60,61], which can alleviate endolymphatic hydrops in the inner ear. Berberine in Phellodendron bark has effects on cyclooxygenase-2, which plays a key role in prostaglandin synthesis, resulting in anti-inflammatory activity[62], while vanillin in Gastrodia Tuber has been shown to protect hippocampal CA1 neurons against ischemic cell death and to produce a significant increase in neuronal survival and antioxidant activity against lipid peroxidation[63], which can protect against brain neuronal injury via inner ear damage. Moreover, vanillin in Gastrodia Tuber, ginsenosides in ginseng, and atractylenolide III in Atractylodes Rhizome have antidepressant effects[59,64,65], which can prevent worsening of...
Table 4 Head-up tilt test factors related to Niigata persistent postural-perceptual dizziness questionnaire improvement at 2 mo

| Variable | Estimate | SE  | t value | P value |
|----------|----------|-----|---------|---------|
| (Intercept) | -16.8 | 4.78 | -3.51 | 0.004<sup>a</sup> |
| Age | 0.01 | 0.006 | 2.04 | 0.06 |
| Sex | -0.78 | 0.60 | -1.31 | 0.21 |
| INOH | | | | |
| Immediate change ratio (dBP) | 2.41 | 1.42 | 1.69 | 0.11 |
| Immediate change ratio (sBP) | 2.82 | 1.72 | 1.63 | 0.13 |
| Delayed OH | | | | |
| Delayed change ratio (dBP) | 1.36 | 0.94 | 1.44 | 0.17 |
| Delayed change ratio (sBP) | 1.67 | 1.04 | 1.60 | 0.13 |
| PoTS | | | | |
| Immediate change ratio (HR) | 4.39 | 1.40 | 3.13 | 0.009<sup>b</sup> |
| Parasympathetic nervous system | | | | |
| Immediate change ratio (CVRR) | 0.88 | 0.37 | 2.36 | 0.03<sup>a</sup> |
| Delayed change ratio (HF) | 2.27 | 0.68 | 3.34 | 0.006<sup>b</sup> |
| Sympathetic nervous system | | | | |
| Immediate change ratio (L/H) | 0.09 | 0.07 | 1.21 | 0.24 |
| Delayed change ratio (L/H) | 0.59 | 0.26 | 2.26 | 0.04<sup>a</sup> |

<sup>a</sup>P < 0.05.
<sup>b</sup>P < 0.01.

Residual standard error = 0.29 (df = 11); multiple R-squared = 0.66; adjusted R-squared = 0.32; F-statistic = 1.95 (df, 11 and 11); P value = 0.14; Akaike information criterion = -49.7. HF: High-frequency component; L/H: Low-frequency component/high-frequency component; CVRR: Coefficient of variation of the R-R interval; INOH: Instantaneous orthostatic hypotension; OH: Orthostatic hypotension; PoTS: Postural tachycardia syndrome; NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness.

Table 5 Questionnaire survey factors related to Niigata persistent postural-perceptual dizziness questionnaire improvement at 2 mo

| Variables | Estimate | SE  | t value | P value |
|-----------|----------|-----|---------|---------|
| (Intercept) | 1.28 | 0.22 | 5.59 | 0.00002<sup>c</sup> |
| DHI-E | -0.03 | 0.01 | 2.56 | 0.01<sup>a</sup> |
| DHI-F | -0.02 | 0.01 | -1.86 | 0.07 |
| HADS-A | -0.05 | 0.01 | -3.30 | 0.003<sup>b</sup> |
| PSQI | -0.05 | 0.01 | -2.80 | 0.01<sup>a</sup> |

<sup>a</sup>P < 0.05.
<sup>b</sup>P < 0.01.
<sup>c</sup>P < 0.001.

Residual standard error = 0.27 (df = 19); multiple R-squared = 0.51; adjusted R-squared = 0.41; F-statistic = 5.02 (df, 4 and 19); P value = 0.006; Akaike information criterion = -57.4. DHI-E: Dizziness handicap index–emotional; DHI-F: Dizziness handicap index–functional; HADS-A: Hospital anxiety and depression scale-anxiety; PSQI: Pittsburg sleep quality index.

PPPD symptoms[1]. Hesperidin in Citrus unshiu peel, atractyleholide III in Atractylodes rhizome, and ginsenosides in ginseng activate cyclic AMP response element binding protein (CREB)/the brain-derived neurotrophic factor (BDNF) pathway in the hippocampus[59,64,65], similar to the pharmacological actions of SSRIs/SSNIs on serotonergic neurotransmission (5-HT-CRF pathway)[66,67], which increases ghrelin signaling and activates the BDNF/trkB/CREB pathway in the cerebral cortex and vestibular nucleus[68]. Thus, in PPPD patients, HBT is hypothesized to have an anti-diuretic effect in the inner ear, consistent with strategy 1, while CREB-BDNF activation in the hippocampus, cerebral cortex, and vestibular nucleus has the same action as SSRIs/SSNIs, which has therapeutic effects in PPPD[55,69], and is consistent with strategies 2 and 3. In addition, gastroesophageal vagal nerve activation by HBT[58,70] might produce feedback resulting in somatosensory suppression via the autonomic nervous system in the hypothalamus, anterior cingulate gyrus, and insular cortex[71,72], resulting in sensory reweighting to establish a balance between the systems and increased tolerance to the perceived
Figure 3 Comparison of rate of improvement and Niigata persistent postural-perceptual dizziness questionnaire scores between groups. A: Comparisons between groups revealed significant differences in the rate of Niigata persistent postural-perceptual dizziness questionnaire (NPQ) improvement (1 mo, $P = 0.16$; 2 mo, $P = 0.009$); B-E: There were significant differences in NPQ total scores, upright posture/walking scores, and movement scores at 2 mo between groups; B: Total score: Baseline, $P > 0.99$; 1 mo, $P = 0.89$; 2 mo, $P = 0.02$; C: Upright posture/walking: Baseline, $P > 0.99$; 1 mo, $P = 0.21$; 2 mo, $P = 0.005$; D: Movement: Baseline, $P > 0.99$; 1 mo, $P = 0.87$; 2 mo, $P = 0.03$; E: Visual stimulation: Baseline, $P = 0.11$; 1 mo, $P = 0.99$; 2 mo, $P = 0.06$. $^aP < 0.05$; $^bP < 0.01$; $^cP < 0.001$. Data represent mean and standard error (vertical bars). NPQ: Niigata PPPD questionnaire; HBT: Hangebyakujutsutemmato; PPPD: Persistent postural-perceptual dizziness; NS: Not significant.

We performed multiple regression analysis to identify patients with PPPD who responded to HBT. Our results showed that PPPD with autonomic dysfunction; body balance dysfunction related to vestibular (ACF), visual (ARF), or somatosensory (VFCC and ACF) factors[41]; unilateral CP, anxiety, and poor sleep quality at baseline were characteristics of HBT responders. In particular, changes in HR and CVRR with upright posture and delayed changes in HF and LF/HF during standing, which are deeply related to autonomic function, were important factors for HBT responses in PPPD patients. These results suggest that the effect of HBT in patients with PPPD might be to improve antecedent vestibular disease and autonomic dysfunction modified by mood disorders. Therefore, our hypothesis regarding the mechanism of action of HBT in PPPD (strategies 1-3) might be correct.

Limitations

There are several limitations to this study. First, since HBT contains a variety of herbal ingredients, it is difficult to ascertain which ingredients affected PPPD. Second, patients were not treated solely with HBT, but also with non-Kampo drugs for vertigo/dizziness and VR. Third, the patient population in this study was small. Randomized blinded trials with a non-HBT treatment group are needed to provide more robust evidence. Fourth, only subjective investigator-rated and/or patient-self-reported
outcome measures were used as study endpoints, potentially introducing various biases. Markers for the prognosis of PPPD are necessary.

CONCLUSION
The present study is the first to demonstrate that HBT is an effective adjunct treatment for PPPD. It was hypothesized that several herbal ingredients in HBT could improve diuretic conditions in the inner ear, the functionality of the CREB-BDNF pathway in the brain, and digestive dysfunction, resulting in sensory reweighting to establish balance of the systems involved in PPPD. PPPD patients who are HBT responders might have antecedent vestibular disease and modified autonomic dysfunction as a result of mood disorders.

ARTICLE HIGHLIGHTS
Research background
Persistent postural-perceptual dizziness (PPPD) is characterized by a shift in processing spatial orientation information to favor visual or somatosensory information over vestibular inputs as well as failure of higher cortical mechanisms.

Research motivation
To date, no potential therapies for PPPD have been evaluated in randomized controlled clinical trials or been approved as a cure for this condition. Hangebyakujututemmato (HBT) has been reported as a potential treatment for PPPD.

Research objectives
Our aim was to examine the efficacy of HBT in PPPD.

Research methods
Patients were administered HBT extract (7.5 g/day), or not, for 3 mo. Assessments such as equilibrium tests were performed at baseline and every month after the start of the study. Multivariate regression analysis was performed to identify HBT responders.

Research results
The Kampo medicine, HBT, was effective as an adjunctive therapy for PPPD. In addition, HBT responders had autonomic dysfunction, unstable balance, semicircular canal paresis, anxiety, and poor sleep quality at baseline.

Research conclusions
HBT may be an effective adjunct treatment for PPPD. We identified the characteristics of the HBT responders.

Research perspectives
According to our results, and previous reports, several herbal ingredients in HBT might improve autonomic function and the cyclic AMP response element binding protein/the brain-derived neurotrophic factor pathway, resulting in sensory reweighting to establish a balance between the systems involved in PPPD.

FOOTNOTES
Author contributions: Miwa T contributed to the investigation, project administration, methodology, software, resources, visualization, writing–original draft, data curation, formal analysis, supervision, conceptualization, validation, writing–review and editing; Kanemaru SI contributed to the methodology, supervision, conceptualization. All authors approved the final version of the manuscript.

Institutional review board statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Kitano Hospital (protocol code 2104002 for the approval).

Informed consent statement: Written informed consent was obtained from all participants prior to study inclusion.

Conflict-of-interest statement: The authors declare no conflict of interest.
REFERENCES

1. Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T. Bronstein A. Diagnostic criteria for persistent postural-perceptual dizziness (PPPDD): Consensus document of the committee for the Classification of Vestibular Disorders of the Bárány Society. J Vestib Res 2017; 27: 191-208 [PMID: 29036855 DOI: 10.3233/JES-170622]

2. Huppert D, Strupp M, Rettinger N, Hecht J, Brandt T. Phobic postural vertigo—a long-term follow-up (5 to 15 years) of 106 patients. J Neurol 2005; 252: 564-569 [PMID: 15742115 DOI: 10.1007/s00415-005-0699-z]

3. Popkirov S, Stone J, Hollle-Lee D. Treatment of Persistent Postural-Perceptual Dizziness (PPPDD) and Related Disorders. Curr Treat Options Neurol 2018; 20: 50 [PMID: 30315375 DOI: 10.1007/s11940-018-0553-0]

4. Staab JP. Chronic subjective dizziness. Continuum (Minneapolis Minn) 2012; 18: 1118-1141 [PMID: 23042063 DOI: 10.1212/01.CNS.0000421622.56525.S8]

5. Nada EH, Ibraheem OA, Hassaan MR. Vestibular Rehabilitation Therapy Outcomes in Patients With Persistent Postural-Perceptual Dizziness. Ann Otol Rhinol Laryngol 2019; 128: 323-329 [PMID: 30607985 DOI: 10.1177/0003489418823017]

6. Yardley L, Barker F, Muller I, Turner D, Kirby S, Mullee M, Morris A, Little P. Clinical and cost effectiveness of booklet based vestibular rehabilitation for chronic dizziness in primary care: single blind, parallel group, pragmatic, randomised controlled trial. BMJ 2012; 344: e2237 [PMID: 22674920 DOI: 10.1136/bmj.e2237]

7. Holmberg J, Karlberg M, Harlacher M, Rivano-Fischer M, Magnusson M. Treatment of phobic postural vertigo. A controlled study of cognitive-behavioral therapy and self-controlled desensitization. J Neurol 2006; 253: 500-506 [PMID: 16362533 DOI: 10.1007/s00415-005-0050-6]

8. Edelman S, Mahoney AE, Cremer PD. Cognitive behavior therapy for chronic subjective dizziness: a randomized, controlled trial. Am J Otolarngol 2012; 33: 395-401 [PMID: 22104568 DOI: 10.1016/j.amjoto.2011.10.009]

9. Tschán R, Eckhardt-Henn A, Scheurich V, Best C, Dieterich M, Beutel M. [Steadfast—effectiveness of a cognitive-behavioral self-management program for patients with somatof orm vertigo and dizziness]. Psychother Psychosom Med Psychol 2012; 62: 111-119 [PMID: 22407528 DOI: 10.1055/s-0032-1304575]

10. Eren OE, Filippopulos F, Sönmez K, Möhwald K, Straube A, Schöberl F. Non-invasive vagus nerve stimulation significantly improves quality of life in patients with persistent postural-perceptual dizziness. J Neurol 2018; 265: 63-69 [PMID: 29785522 DOI: 10.1007/s00415-018-8894-x]

11. Kimura T, Yamanaka N, Kuki K, Saito T, Yoda J, Hotomi M, Kawaue A, Tamaki K, Shimada J, Fujiwara K, Nishimura Y. Kampo treatments for vertigo/dizziness patients. Jibi to Rinsho 1999; 45: 443-449 [DOI: 10.11334/jibiri1994.45.443]

12. Takahashi Y, Okamura R, Ishii T. Effect of TSUMURA & Co. Hanka-hakujutsu-tenma-to on patients with dizziness. Jibi to Rinsho 2019; 45: DOI: 10.11344/jibiri1954.45.443

13. Murakami A, Kobayashi D, Kubota T, Zukeyma N, Mukae H, Furusyo N, Kaneu M, Shimazoe T. Bioelectrical Impedance Analysis (BIA) of the association of the Japanese Kampo concept “Suidoku” (fluid disturbance) and the body composition of women. BMC Complement Altern Med 2016; 16: 405 [PMID: 27770788 DOI: 10.1186/s12906-016-1373-9]

14. Arai M. Study of combination therapy of vestibular rehabilitation and hangebakujutsutennma for dizziness. Kampo New Ther 2015; 24: 233-240

15. Okamura N, Takayama K, Kaita T. Effect of Goreisan on diarrhea model mouse induced by saline purgative. Kampo Med 2009; 60: 493-501 [DOI: 10.3937/kampomed.60.493]

16. Yamagawa M, Inagaki M, Harada T, Uki K, Sakakura Y, Miyoshi Y. Chinese herbal therapy (Kampo) for vertigo and dizziness. Practica Oto-Rhino-Laryngolica 1983; 76: 326-327 [DOI: 10.5631/jibirin.76.326]

17. Fujimoto M, Shimada Y. Kampo treatments for vertigo/dizziness patients. Equilib Res 2012; 71: 219-225 [DOI: 10.3757/jer.71.219]

18. Hamaguchi S, Egawa H, Ozawa H, Numata Y, Terashima T, Kimura Y, Ktgjima T. Hangebakujutsutennma can decrease the adverse effects of opioids in chronic pain patients: two case reports. Kampo Med 2015; 66: 327-330 [DOI: 10.3757/kampomed.66.327]
Watanabe K, Moriyama K, Tokumine J, Yorozu T. Effect of hangebyakujututemmatto on pregabalin-induced dizziness in a rat model of neuropathic pain. Traiti-Kampo Med 2019; 6 [DOI: 10.1002/tkm2.1218]

Yugi C, Morita Y, Kitazawa M, Nonomura Y, Yamagishi T, Oshimia S, Izumi S, Takahashi K, Horii A. A Validated Questionnaire to Assess the Severity of Persistent Postural-Perceptive Dizziness (PPPD): The Nigata PPPD Questionnaire (NPPQ). Otol Neurotol 2019; 40: e747-752 [PMID: 31219964 DOI: 10.1097/MTO.0000000000002232]

Ikezono T, Taka A, Nakamura T, Asai M, Ikeda T, Imaizumi S, Shigemori K, Takahashi K, Taki Y, Yamamoto M, Watanabe Y. Diagnostic criteria of balance disorders in Japan (Revised edition, in Japanese). Equilib Res 2017; 76: 233-241 [DOI: 10.3757/jser.76.233]

Komiatsu A. Diagnostic criteria of balance disorders in Japan (In Japanese). Equilib Res 1995; 54: 29-57 [DOI: 10.3757/jser.54.suppl-11_29]

Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990; 116: 424-427 [PMID: 2315323 DOI: 10.1001/archotol.1990.007004000611]

Masuda K, Goto F, Fujii M, Kunihiro T. Investigation of the reliability and validity of Dizziness Handicap Inventory (DHI) translated into Japanese. Equilib Res 2004; 63: 555-563 [DOI: 10.3757/jser.63.555]

Zigmond AS, Smith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-370 [PMID: 6808280 DOI: 10.1111/j.1600-0447.1983.tb09716.x]

Hatta H, Higashi A, Yashiro H, Ozasa K, Hayashi K, Kyotani K, Inokuchi H, Ikeda J, Fujita K, Watanabe Y, Kawai K. A validation of the hospital anxiety and depression scale. Japanese J Psychosom Med 1998; 38: 309-315 [DOI: 10.15064/jppm.38.5.309]

Okuni M. Orthostatic dysregulation in childhood with special reference to the standing electrocardiogram. Jpn Circ J 1963; 27: 200-204 [PMID: 13993892 DOI: 10.1253/jcj.27.200]

Tanaka H, Fujita Y, Takenaka Y, Kajiwara S, Masutani S, Ishizaki Y, Matsushima R, Shiokawa H, Shiota M, Ishitani N, Kajiwara M, Honda K, Task Force of Clinical Guidelines for Child Orthostatic Dysregulation, Japanese Society of Psychosomatic Pediatrics. Japanese clinical guidelines for juvenile orthostatic dystrophic version 1. Pediatr Int 2009; 51: 169-179 [PMID: 19371360 DOI: 10.1111/j.1442-200X.2008.02783.x]

Garybien A, Wood CD, Miller EF, Cramer DB. Diagnostic criteria for grading the severity of acute motion sickness. Aerosp Med 1968; 39: 453-455 [PMID: 5648730]

Doi Y, Minowa M, Uchiyama M, Okawa M, Kim K, Shibui K, Kamei Y. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res 2000; 97: 165-172 [PMID: 11166088 DOI: 10.1016/S0165-1781(00)00232-8]

Buyse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28: 193-213 [PMID: 2748771 DOI: 10.1016/1056-1781(89)90047-4]

Tjernström F, Björkland M, Malmström EM. Romberg ratio in quiet stance posturography--Test to retest reliability. Gait Posture 2015; 42: 27-31 [PMID: 25891528 DOI: 10.1016/j.gaitpost.2014.12.007]

Yasuda T, Miwa T. Foulage test. Protocols to 2021

Yasuda T, Etoh N, Araki Y, Yamada J, Ide R, Ohkawara T, Kunihiro T. A dynamic equilibrium examination on stablomter (Foulage test). Equilib Res 2012; 71: 61-70 [DOI: 10.3757/jser.71.61]

Yasuda T, Etoh N, Araki Y, Souma K, Kunihiro T. The new method of plotting steps in foulage test. Equilib Res 2016; 75: 22-26 [DOI: 10.3757/jser.75.22]

Miwa T, Yasuda T. Dynamic equilibrium examination utilizing a six-axis sensor during the foulage test. Equilib Res 2020; 78: 80-87 [DOI: 10.3757/jser.79.80]

Murofushi T, Kaga K. Vestibular evoked myogenic potential. Its basics and clinical applications. Tokyo: Springer Japan, 2009

Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular-evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. Clin Neurophysiol 2007; 118: 2745-2751 [PMID: 17905655 DOI: 10.1016/j.clinph.2007.08.005]

Midorikawa C, Takahashi M, Tsujita N, Hoshikawa H. [A simple cold caloric test]. Nihon Jibiinkoka Gakkai Kaiho 1984; 87: 1111-1119 [PMID: 6520644 DOI: 10.3950/jibiinkoka.87.1111]

Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. J Intern Med 2013; 273: 322-335 [PMID: 23216860 DOI: 10.1111/joim.12021]

Fujimoto C, Murofushi T, Chihara Y, Ushio M, Sugawara K, Yamaguchi T, Yamasoba T, Iwasaki S. Assessment of diagnostic accuracy of foam posturography for peripheral vestibular disorders: analysis of parameters related to visual and somatosensory dependence. Clin Neurophysiol 2009; 120: 1408-1414 [PMID: 19520601 DOI: 10.1016/j.clinph.2009.05.002]

Yasuda T, Etoh N, Araki Y, Ohkawara T, Kunihiro T. Trial study on a dynamic equilibrium examination on stablomter (foulage test)- clinical study in patients with dizziness. Equilib Res 2013; 72: 22-29 [DOI: 10.3757/jser.72.22]

Yasuda T, Etoh N, Araki Y, Souma K, Kunihiro T. Attempt to measure the rotatory angle in foulage test. Equilib Res 2016; 75: 41-46 [DOI: 10.3757/jser.75.41]

Yasuda T, Etoh N, Araki Y, Kunihiro T. Clinical course of a severe vertigo attack in patients with Meniere’s disease or delayed hydrops investigated by a new dynamic equilibrium examination (Foulage test). Equilib Res 2013; 72: 163-170 [DOI: 10.3757/jser.72.163]

Rosenberg BM, Colebatch JG, Young AS, Govender S, Welgampola MS. Vestibular evoked myogenic potentials in practice: Methods, pitfalls and clinical applications. Clin Neurophysiol Pract 2019; 4: 47-68 [PMID: 30949613 DOI: 10.1016/j.cnp.2019.01.005]

Fife TD, Colebatch JG, Kerber KA, Brantberg K, Strupp M, Lee H, Walker MF, Ashman E, Fletcher J, Callaghan B, Gloss DS 2nd. Practice guideline: Cervical and ocular vestibular evoked myogenic potential testing: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology
Miwa T et al. Hangebyakujuttemattu for PPPD treatment

2017; 89: 2288-2296 [PMID: 29093067 DOI: 10.1212/WNL.0000000000004690]

Miwa T. Vestibular Function After the 2016 Kumamoto Earthquakes: A Retrospective Chart Review. Front Neurol 2020; 11: 626613 [PMID: 33551981 DOI: 10.3389/feur.2020.626613]

Jongkees LB, Maas JP, Philipsoonz AJ. Clinical nystagmography. A detailed study of electro-nystagmography in 341 patients with vertigo. Pract Otorhinolaryngol (Basel) 1962; 24: 65-93 [PMID: 14452374]

Gakkei NJS. Jiritsu shinkei kō/kensa. 5th ed. Tokyo: Bunkōdō

Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. Control Clin Trials 1990; 11: 116-128 [PMID: 2161310 DOI: 10.1016/0197-2456(90)90005-M]

Indovina I, Riccelli R, Chiarella G, Petrolo C, Augmier A, Giofre L, Lacquanti F, Staab JP, Passamonti L. Role of the Insula and Vestibular System in Patients with Chronic Subjective Dizziness: An fMRI Study Using Sound-Evoked Vestibular Stimulation. Front Behav Neurosci 2015; 9: 334 [PMID: 26499853 DOI: 10.3389/fnbeh.2015.00334]

Söhsten E, Bittar RS, Staab JP. Posturographic profile of patients with persistent postural-perceptual dizziness on the sensory organization test. J Vestib Res 2016; 26: 319-326 [PMID: 27928386 DOI: 10.3233/VIS-160583]

Riccelli R, Passamonti L, Toschi N, Nigro S, Chiarella G, Petrolo C, Lacquanti F, Staab JP, Indovina I. Altered Insular and Occipital Responses to Simulated Vertical Self-Motion in Patients with Persistent Postural-Perceptual Dizziness. Front Neurol 2017; 8: 529 [PMID: 29089920 DOI: 10.3389/fneur.2017.00529]

Lee JO, Lee ES, Kim JS, Lee YB, Jeong Y, Choi BS, Kim JH, Staab JP. Altered brain function in persistent postural perceptual dizziness: A study on resting state connectivity. Hum Brain Mapp 2018; 39: 3340-3353 [PMID: 29656497 DOI: 10.1002/hbm.24800]

Staab JP, Rohe DE, Eggers SD, Shepard NT. Anxious, introverted personality traits in patients with chronic subjective dizziness. J Psychosom Res 2014; 76: 80-83 [PMID: 24360146 DOI: 10.1016/j.jpsychores.2013.11.008]

Rascol O, Hain TC, Brefel C, Benazet M, Clanet M, Montastruc JL. Antivertigo medications and drug-induced vertigo. A pharmacological review. Drugs 1995; 50: 777-791 [PMID: 8586026 DOI: 10.2165/00003495-199550050-00002]

Kudoh C, Arita R, Honda M, Kishi T, Komatsu Y, Asou H, Mimura M. Effect of nippi/yoito, a Kampo (traditional Japanese) medicine, on cognitive impairment and depression in patients with Alzheimer's disease: 2 years of observation. Psychogeriatrics 2016; 16: 85-92 [PMID: 25918972 DOI: 10.1111/psyg.12125]

Huang Y, Patil MJ, Yu M, Liptak P, Undem BJ, Dong X, Wang G, Yu S. Effects of ginger constituent 6-shogaol on gastroesophageal vagal afferent C-fibers. Neurogastroenterol Motil 2019; 31: e13585 [PMID: 30947390 DOI: 10.1111/nmo.13585]

Izumi H, Sasaki Y, Yahagi Y, Shinoda Y, Fujita N, Yomoda S, Fukunaga K. Memory improvement by Yokokansankachimpihange and Atractylenolide III in the olfactory bulbectomized mice. Adv Alzheimer’s Dis 2016; 5: 35-45 [DOI: 10.4236/aad.2016.52003]

Wang P, Song T, Shi R, He M, Wang R, Lv J, Jiang M. Triterpenoids From Alisma Species: Phytochemistry, Structure Modification, and Bioactivities. Front Chem 2020; 8: 363 [PMID: 36243239 DOI: 10.3389/fchem.2020.00363]

Ne A, Chao Y, Zhang X, Jia W, Zhou Z, Zhu C. Phytochemistry and Pharmacological Activities of Wolfiporia cocos (F.A. Wolf) Ryvarden & Gilb. Front Pharmacol 2020; 11: 505249 [PMID: 33071776 DOI: 10.3389/fphar.2020.505249]

Kuo CL, Chi CW, Liu TY. The anti-inflammatory potential of berberine in vitro and in vivo. Cancer Lett 2004; 203: 127-137 [PMID: 14732220 DOI: 10.1016/j.canlet.2003.09.002]

Kim BH, Hwang IK, Won MH. Vanillin, 4-hydroxybenzyl aldehyde and 4-hydroxybenzyl alcohol prevent hippocampal CA1 cell death following global ischemia. Brain Res Rev 2007; 585: 130-141 [PMID: 17945203 DOI: 10.1016/j.brainres.2007.08.066]

Ito A, Shin N, Tsuchida T, Okubo T, Norimoto H. Antianxiety-like effects of Chimpi (dried citrus peels) in the elevated open-platform test. Molecules 2013; 18: 10014-10023 [PMID: 23966085 DOI: 10.3390/molecules18081014]

Rokot NT, Kairupan TS, Cheng KC, Runtuwene J, Kapantow NH, Amitani M, Morinaga A, Amitani H, Asakawa A, Inui A. A Role of Ginseng and Its Constituents in the Treatment of Central Nervous System Disorders. Evid Based Complement Alternat Med 2016; 2016: 2614742 [DOI: 10.1155/2016/2614742]

Peng Q, Masuda N, Jiang M, Li Q, Zhao M, Ross CA, Duan W. The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 Huntington's disease mouse model. Exp Neurol 2008; 210: 154-163 [PMID: 18096160 DOI: 10.1016/j.expneurol.2007.10.015]

Fuji H, Shimizu K, Shinogori H, Hashimoto M, Miwa T, Sugahara K, Yamashita H. Selective serotonin reuptake inhibitor (SSRI) and vestibular function. Equilib Res 2020; 79: 12-19 [DOI: 10.3757/jser.79.12]
