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Otolaryngology -- Head and Neck Surgery 2014 151: 321 originally published online 25 April 2014
DOI: 10.1177/0194599814533075

The online version of this article can be found at:
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Utricular Dysfunction in Refractory Benign Paroxysmal Positional Vertigo

Simon I. Angeli, MD1, Marianne Abouyared, MD1, Hillary Snapp, AuD1, and Daniel Jethanamest, MD2

Abstract

Objective. To determine the prevalence of otolith dysfunction in patients with refractory benign paroxysmal positional vertigo (BPPV).

Study Design. Unmatched case control.

Setting. Tertiary care institution.

Subjects and Methods. Patients included were diagnosed with BPPV, failed initial in-office canalith repositioning maneuvers (CRMs), and completed vestibular testing and vestibular rehabilitation (n = 40). Refractory BPPV (n = 19) was defined in patients whose symptoms did not resolve despite vestibular rehabilitation. These patients were compared with a control group of those with nonrefractory BPPV (n = 21) for results of a caloric test, cervical vestibular evoked myogenic potential (cVEMP), and subjective visual vertical (SVV).

Results. Forty-six of 251 patients failed initial treatment with in-office CRM. Forty patients met inclusion criteria. There was no significant difference between the cases (refractory BPPV) and controls (nonrefractory BPPV) in terms of age, duration of symptoms, laterality of BPPV, and BPPV rehabilitation. These patients were compared with a control group of those with nonrefractory BPPV (n = 21) for results of a caloric test, cervical vestibular evoked myogenic potential (cVEMP), and subjective visual vertical (SVV).

Results. Forty-six of 251 patients failed initial treatment with in-office CRM. Forty patients met inclusion criteria. There was no significant difference between the cases (refractory BPPV) and controls (nonrefractory BPPV) (n = 21) in terms of age, duration of symptoms, laterality of BPPV, and BPPV symptoms. There was no difference in the prevalence of caloric weakness and cVEMP abnormalities (P > .05), with odds ratios (ORs [95% confidence interval (CI)]) of having abnormal results among cases vs controls of 1.1818 (0.3329-4.1954) and 4.3846 (0.7627-25.2048), for caloric and cVEMP, respectively. Abnormal eccentric SVV was more prevalent in refractory BPPV cases (58%) than in controls (14%) (P < .0072). The OR (95% CI) of having abnormal SVV was 8.25 (1.7967-37.8822) higher among patients with refractory BPPV than those with nonrefractory BPPV.

Conclusion. Patients with refractory BPPV are more likely to have abnormal eccentric SVV and thus underlying utricular dysfunction. This finding is important to take into account when designing rehabilitation strategies for patients with BPPV who fail CRM.

Keywords

subjective visual vertical, vestibular testing, refractory benign paroxysmal positional vertigo, BPPV, vertigo, otolith dysfunction, utricle, saccule

Received October 23, 2013; revised March 13, 2014; accepted April 4, 2014.

Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder in adults, present in 42% of patients with vertigo.1 Clinical features include brief attacks of vertigo associated with specific head movements and nystagmus that begins after a 5- to 20-second latency period, resolves within 60 seconds, is fatigable with repeated provocative maneuvers, and reverses direction once seated upright.1 The posterior semicircular canal is most commonly involved.

Benign paroxysmal positional vertigo is best explained by the canalithiasis theory, whereby dislodged otoconia from the utricle gravitate toward the ampullated ends of the semicircular canals. Head movement and thus canal rotation lead to otoconia deflection of the cupula, causing vertigo. Although canalithiasis is a widely accepted explanation for BPPV, our knowledge of the pathophysiologic processes that lead to the dislodgement of otoconia from the utricle is limited. Human temporal bone studies have shown degeneration of the utricle in BPPV cases associated with vestibular neuronitis and trauma and a significant decrease in the utricular otoconia in elderly patients, supporting clinical observations that these are risk factors for BPPV.2,3 However, at least half of BPPV cases appear to be idiopathic.4

Canalith repositioning maneuvers (CRMs) have been reported to resolve vertigo 85% of the time.5 The goal of these maneuvers is to reposition the dislodged floating otoconia from the ampullated ends of the semicircular canals. Despite resolution of their positional vertigo, many patients continue to experience symptoms of imbalance and altered visual-vestibular interaction. Degeneration of the utricular macula...
and thus otolith dysfunction in these patients has been attributed as the cause for the prolonged imbalance. Subjective visual vertical (SVV) testing during eccentric rotation is a reliable measure of utricular dysfunction, and patients with unilateral BPPV have been shown to have abnormalities of the SVV during eccentric rotation compared with controls. Furthermore, ocular vestibular evoked myogenic potentials (oVEMP) and cervical vestibular evoked myogenic potentials (cVEMP) are described to assess the function of the utricle and saccule, respectively. Interestingly, in a group of patients with posterior semicircular canal BPPV, there was a higher incidence of oVEMP abnormalities, further indicating that utricular dysfunction is a feature of BPPV.

Some patients with BPPV have refractory vertigo despite multiple CRM treatments. These patients have been shown to benefit from vestibular rehabilitation programs that reduce visual-vestibular conflict and eliminate symptoms by promoting habituation and adaptive mechanisms. We hypothesize that patients with refractory BPPV have associated vestibulopathies, mainly utricular dysfunction. The purpose of our study is to show this association between utricular dysfunction and refractory BPPV. This relationship is important to identify since specific rehabilitation strategies can then be designed to help relieve these patients’ symptoms.

**Methods**

We reviewed medical records of adult patients who presented to the neurotology clinic between January 2010 and December 2012 with the primary complaint of positional vertigo and a diagnosis of BPPV by established criteria. This study’s protocol was approved by the University of Miami Institutional Review Board. Patients underwent a complete history and neurotologic physical examination that included Dix-Hallpike examination with Frenzel’s lenses in partial darkness. Benign paroxysmal positional vertigo was diagnosed after a positive Dix-Hallpike maneuver during the first visit; immediately after diagnosis, patients underwent CRM therapy. If the vertigo and nystagmus resolved, the patients were discharged. Patients whose vertigo persisted despite multiple CRMs during the initial visit were referred for vestibular rehabilitation and vestibular testing, and a follow-up appointment was scheduled in 3 to 5 weeks. Data collected included demographics, symptoms at presentation, affected side, and response to a 3- to 5-week trial of vestibular rehabilitation that included CRM and BPPV-specific habituation exercises.

**Figure 1** shows the patients’ management flow. A total of 251 patients with BPPV were seen during the study period, 17 of whom were not included in the analyses due to incomplete medical records, resulting in 234 cases for analyses. In-office CRM was successful in 188 of 234 patients (80%). The remaining 46 patients failed CRM therapy at the initial visit and consequently were referred for additional treatment and vestibular testing. The inclusion criteria were (1) age 18 years or older, (2) diagnosis of BPPV affecting the posterior semicircular canal singly or in combination with other canals, (3) failure to suppress the patients’ vertigo and nystagmus with CRM performed at the initial visit, and (4) complete vestibular testing battery, including videonystagmography (VNG), SVV, and cVEMP. Subjects were excluded if they did not meet the inclusion criteria (1 case with incomplete testing) or had conditions...
testing was performed at 6 frequencies ranging from 0.01 to 0.32 Hz. The maximum slow-phase velocity (SPV) of nystagmus was calculated for each set of tests and analyzed using the manufacturer’s normative data. Abnormal nystagmus response was 30% or greater using Jongkees’s formula. Abnormal responses in the rotary chair test were considered diagnostic of nonlocalizing peripheral vestibulopathy if the results for VOR phase, gain, and symmetry fell outside 2 standard deviations from the mean for at least 2 adjacent frequencies of stimulation.

Subjective visual vertical testing was performed with the patients in the seated position on the rotating Barany chair. To stimulate each utricle separately, patients were rotated about a vertical axis at a constant angular rate of 300 degrees per second until cessation of the VOR. While maintaining a constant velocity, the axis of the chair was moved 3.85 cm toward the tested side. Thus, the eccentric labyrinth is exposed to centrifugal and gravitational force while the inner labyrinth is situated in the center of the rotational axis and free of any centrifugal force. This results in a change of the gravito-inertial vertical of 11 degrees at the eccentric labyrinth, and correspondingly, the SVV is deviated toward the opposite side of the eccentric ear. To test SVV, the patients were asked to rotate a laser line bar (Pursuit Tracker; Neuro Kinetics, Inc, Pittsburgh, Pennsylvania) clockwise or counterclockwise to the position they perceived as vertical, first before eccentric rotation and then during eccentric rotation to each side. When normal subjects are rotated toward one side, they would move the bar toward the opposite side until the bar is very close to the gravitational vertical; similarly, when subjects with unilateral utricular dysfunction are rotated toward the healthy side, they would move the bar toward the lesion (opposite) side approaching the gravitational vertical. Conversely, when subjects with unilateral utricular dysfunction are rotated toward the affected side, they would move the bar less toward the opposite side (healthy side) or even away from the healthy side and instead toward the affected side, because the affected utricle cannot generate enough function to perceive the gravito-inertial tilt.

The SVV is defined as the set angle between the laser bar and the true gravitational vertical. The SVV was classified as abnormal when the median angle value after 4 trials for each ear was outside the 5% to 95% normal range. Accordingly, SVV estimates during eccentric centrifugation allowed the patient’s characterization into 4 groups: (1) bilateral normal, (2) unilateral ipsilesional (abnormal SVV in the same side as BPPV), (3) unilateral contralesional (abnormal SVV in the side opposite to the side of BPPV), and (4) bilateral abnormal. The prevalence of abnormal SVV (categories 2, 3, and 4) was compared between the groups of patients with refractory vs nonrefractory BPPV.

Saccular function was estimated by obtaining cVEMP. A single-channel recording montage was used with the active electrode placed at the recording sternocleidomastoid muscle and the ground electrode placed at the contralateral sternocleidomastoid muscle. As acoustic stimuli, air-conducted 500-Hz short tone bursts (125 dB sound pressure level [SPL], duration of 5 ms) were presented ipsilaterally through insert earphones (Etymotic Research, Elk Grove Village, Illinois) at a stimulation rate of 5 Hz, with up to 200 stimulations per ear. While turning their head, subjects in the supine position were instructed to raise their head to contract the ipsilateral sternocleidomastoid muscle and maintain constant tonic activation for the duration of the acoustic stimulus. Electromyography signals were amplified and band-filtered between 30 and 3000 Hz (Navigator Pro AEP system; Bio-Logic, Mundelein, Illinois), and the latency and amplitude values of the first biphasic responses (p13-n23) of a minimum of 2 cVEMP responses were analyzed. An abnormal response was when the biphasic response was absent or when the interaural amplitude difference was greater than 33%.

Descriptive statistics were used for prevalence estimates of BPPV side and response to treatment in this cohort. Prevalence of abnormal caloric testing, SVV, and cVEMP were individually estimated for both groups (refractory BPPV and nonrefractory BPPV). Intergroup comparisons were done by Pearson χ² or Fisher exact test and by calculating the odds ratio (OR) with the JMP IN 11.0 for Mac (SAS Institute, Belmont, California).
Results

Table 1 shows the distribution of demographic and clinical data. There were no significant differences between the groups for age at presentation, sex, side of lesion, and duration of symptoms before presentation. All 40 patients reported positional rotary vertigo as expected for BPPV, but some had additional symptoms. Twenty patients complained of rotary vertigo alone, 11 had vertigo and imbalance, 6 had vertigo and “linear symptoms” (i.e., sensation of walking on clouds, side-to-side or back-to-forth translations), and 3 had vertigo and lightheadedness. There were no differences between the groups in terms of the prevalence of type of symptoms ($\chi^2$, n = 40, df = 3, $P$ = .2427).

Videonystagmography testing was completed in all patients. Oculomotors were within normal limits in all patients. No patients had spontaneous nystagmus. During Hallpike testing of the VNG, 36 patients had geotropic rotary nystagmus consistent with BPPV of the posterior semicircular canal, 3 had combined posterior and anterior semicircular canal BPPV, and 1 had combined posterior and horizontal semicircular canal BPPV. There was no difference in the prevalence of single vs multicanal BPPV between the groups (Fisher exact test, $P$ = 1.0). The odds of having an abnormal cVEMP for cases was 4.3846 (95% CI, 0.7626-25.2048) higher than for controls. Abnormal SVV was found in 35% (14/40) of the cohort, with a prevalence of 58% (11/19) in cases and 14% (3/21) in controls (Fisher exact test, $P$ = .0072). The odds of having abnormal eccentric SVV results was 8 times higher among patients with refractory BPPV than in controls (OR, 8.25; 95% CI, 1.7967-37.8822).

Discussion

In our cohort, abnormal eccentric SVV was more common in patients with refractory BPPV, with a prevalence of 58% and 14% in the refractory and nonrefractory groups, respectively. The odds of having abnormal eccentric SVV was 8 times higher in patients with refractory BPPV than in controls. Benign paroxysmal positional vertigo has been associated with utricular dysfunction, as indicated by abnormal SVV on eccentric rotation and abnormal oVEMP.8,10 Abnormal otolith-ocular reflex has also been displayed by patients with BPPV, further pointing to the presence of abnormal utricular dysfunction in these patients.6 However, our series is the first to suggest that utricular dysfunction is more prevalent in patients with refractory BPPV. In contrast, we did not demonstrate a difference in the prevalence of abnormal calorics and cVEMP between cases and controls, given than the value of 1.0 for the OR estimates fell within the 95% CI estimate for both tests. Additional studies with a larger number of patients and/or prospective design will be needed to confirm these findings.

It is important to delineate which historical or physical examination findings indicate a patient is at risk for refractory BPPV to more efficiently diagnose and treat these patients. Sato et al2 showed that Dix-Hallpike on day 7 after a single Epley maneuver was more likely to remain positive
in patients with head trauma or prolonged bed rest compared with patients with idiopathic BPPV. Advanced age and structural abnormalities of the inner ear have also been examined as potential risk factors for refractory BPPV. Horii et al examined 3-dimensionally reconstructed magnetic resonance imaging (MRI) scans of patients with intractable BPPV and compared the images with those of control volunteers. Findings of filling defects, indicating canal narrowing, were more prevalent in patients with intractable BPPV, and these defects may increase the predilection of otoconia plugging the canal.15 Our population of patients with refractory BPPV had a significant prevalence of vestibular tests abnormalities. Even among patients assigned to the “nonrefractory” group, caloric weakness was found in 38%, abnormal cVEMP in 10%, and abnormal eccentric SVV in 14%. Benign paroxysmal positional vertigo that is recurrent or refractory to initial therapies has also been associated with vestibular neuronitis, Ménière’s disease, and posterior fossa tumors.4 On the basis of these reports and our findings, we speculate that “difficult-to-treat” BPPV may be a clinical entity distinct from the common canalithiasis BPPV syndrome and that associated disorders should be addressed as well.

Since patients with refractory BPPV experience debilitating symptoms that will not resolve with standard CRM, alternative treatment options may be considered. Customized vestibular rehabilitation with a combination of habituation and adaptation exercises has been shown to enhance the success rate of CRM.11 Patients with BPPV with associated utricular dysfunction may also benefit from rehabilitation directed to the adaptation of the utricular/otolith-ocular reflex.16 Patients with BPPV who fail vestibular rehabilitation and are disabled may benefit from surgical options.17,18

The vestibular system is complex and has considerable redundancy. Although BPPV has been traditionally considered a disease of the semicircular canal, there is ample evidence that some cases represent a multisensory disorder. By realizing the role that the utricle and saccule play in the pathophysiology of semicircular canal disorders such as BPPV, our understanding and management of this common disorder will be enhanced. Fluur and Siegborn described interactions between otolith and semicircular canal inputs in oculomotor muscle control. Others have highlighted the role of the utricle and saccule in modulating the VOR during head tilts and translations and modulating the VOR velocity storage mechanism.22,23

We believe it is of clinical significance to identify patients with BPPV and associated utricular dysfunction since these patients may require a treatment regimen that targets the utricle as well. Patients with otolith dysfunction complain of “walking on clouds,” “unsteadiness,” and “being pulled back-to-forth or side-to-side” and are frequently unable to drive a car or work for a long period at a personal computer.24 These manifestations correspond to what has been defined in this study as “linear” symptoms. During attacks of BPPV, rotary vertigo is usually severe and dominates the clinical manifestations, often masquerading as other symptoms. However, patients with BPPV with associated utricular dysfunction may also report otolithic symptoms if systematically asked. This is indeed what we found in this study, as 26% (5/19) of patients with refractory BPPV had linear symptoms and also abnormal SVV in addition to rotary vertigo, compared with 4% (1/21) of patients with nonrefractory BPPV. Consequently, although we agree with the general recommendations that most patients with

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<th>Table 2. Summary of Vestibular Testing Results.</th>
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<tr>
<td>Total, No. (%)</td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Caloric weakness</td>
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<td>Unilateral ipsilateral</td>
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<td>Unilateral contralateral</td>
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<tr>
<td>Total</td>
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<tr>
<td>Abnormal cVEMP</td>
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<td>Unilateral ipsilateral</td>
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<td>Bilateral</td>
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<tr>
<td>Total</td>
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<td>Abnormal SVV with eccentric rotation</td>
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<td>Bilateral</td>
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<td>Total</td>
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Abbreviations: BPPV, benign paroxysmal positional vertigo; CI, confidence interval; cVEMP, cervical vestibular-evoked myogenic potentials; OR, odds ratio; SVV, subjective visual vertical.

\[P = .73; \text{OR, 1.1818; 95% CI, 0.3329-4.1954.}\]

\[P = .12; \text{OR, 4.3846; 95% CI, 0.7627-25.2048.}\]

\[P = .0072; \text{OR, 8.25; 95% CI, 1.7967-37.8822.}\]
BPPV will not need referral for specialized diagnostics and treatment,1 BPPV with CRM-refractory vertigo and/or associated otolithic symptoms should be referred early for testing of utricular function.

What is novel about our study is the fact that most patients with abnormal eccentric SVV were in the refractory BPPV group, suggesting that abnormal utricular function is associated with persistent vestibular symptoms after treatment of the positional vertigo. The clinical corollary is that patients with BPPV who fail an initial attempt at CRM and who have utricular dysfunction may benefit from a customized vestibular rehabilitation strategy that addresses the specific deficit.16

One important limitation of this study is the fact that because this is a retrospective review, the extent of vestibular rehabilitation that the patients underwent after initial CRM could not be uniformly assessed. This could have affected the prevalence of refractory BPPV and the method of selection of the case and control groups. However, considering that 80% of our patients responded to the initial treatment for canalithiasis, subjects in our cohort, in both the refractory BPPV and in the nonrefractory BPPV groups, represent a subset of patients with more difficult-to-treat BPPV than the common canalithiasis cases. Future studies will be designed prospectively with a focus on providing a standardized treatment program and assessing the effect of utricular-specific rehabilitation. Furthermore, although the observed risk of having abnormal eccentric SVV in cases was 8 times higher than in controls, the effect size should be interpreted with caution as the resulting lower limit of the 95% CI approximates the value of 1.0 (1.7967). Finally, our results cannot easily be extrapolated to all patients with BPPV, since most patients will respond to initial treatment and will not be referred for specialized diagnostics.

In summary, our series specifically examines patients with refractory BPPV and assesses their associated utricular function. We found that patients with refractory BPPV had a higher prevalence of abnormal eccentric SVV, thus suggesting a greater prevalence of utricular dysfunction in this subgroup. With this in mind, we recommend that clinicians investigate utricular function with eccentric SVV or other utricular tests on patients with BPPV whose symptoms do not respond to CRM. We propose that these patients would benefit from specifically designed vestibular rehabilitation for their utricular dysfunction.

Author Contributions
Simon I. Angeli, substantial contributions to concept and design, acquisition of data, analysis of data, drafting of article and revising critically, final approval for publication; Marianne Abouyared, acquisition of data, drafting article and revision, final approval of version to be published; Hillary Snapp, concept and design, revising article critically, final approval; Daniel Jethanamest, interpretation of data, revising article critically, final approval.

Disclosures
Competing interests: Simon I. Angeli received a Medtronic research grant unrelated to the present study.

Sponsorships: None.
Funding source: None.

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