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Review Article

Benign Paroxysmal Positional Vertigo: An Integrated Perspective

Kourosh Parham

Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Connecticut Health Center, Farmington, CT 06030-6228, USA

Correspondence should be addressed to Kourosh Parham; parham@neuron.uchc.edu

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Benign paroxysmal positional vertigo (BPPV), the most common cause of dizziness, occurs in all age groups. It presents with vertigo on head movement, but in older patients presentation may be typical and thus accounting for a low recognition rate in the primary care setting. It may be recurrent in up to 50% of cases. BPPV is associated with displacement of fragments of utricular otoconia into the semicircular canals, most commonly the posterior semicircular canal. Otoconia are composed of otoconin and otolin forming the organic matrix on which calcium carbonate mineralizes. Otoconia may fragment with trauma, age, or changes in the physiology of endolymph (e.g., pH and calcium concentration). Presentation varied because otoconia fragments can be displaced into any of the semicircular canals on either (or both) side and may be free floating (canalolithiasis) or attached to the cupula (cupulolithiasis). Most cases of BPPV are idiopathic, but head trauma, otologic disorders, and systemic disease appear to be contributory in a subset. Positional maneuvers are used to diagnose and treat the majority of cases. In rare intractable cases surgical management may be considered. A strong association with osteoporosis suggests that idiopathic BPPV may have diagnostic and management implications beyond that of a purely otologic condition.

1. Epidemiology and Impact

Dizziness arising from vertigo is a common morbidity that adversely affects balance and quality of life. A study of a nationally representative sample of 4,869 adults living in Germany who were screened for moderate or severe dizziness found a prevalence of 22.9% for dizziness/vertigo in the prior 12 months [1]. In that study, the prevalence and incidence of vestibular vertigo were 4.9% and 1.4%, respectively. They also found that, compared to nonvestibular dizziness, vestibular vertigo was more frequently followed by medical consultation, sick leave, interruption of daily activities, and avoidance of leaving the house.

Population studies such as the above consistently show that benign paroxysmal positional vertigo (BPPV) is the most common cause of dizziness [2]. In a large registry that included data collected from 4,294 patients with vertigo in 13 countries generated over a 28-month period (the Registry to Evaluate the Burden of Disease in Vertigo, the so-called REVERT registry) nearly 1/3 were diagnosed to have BPPV [3]. BPPV can occur throughout the lifespan, from childhood [4] into old age. While presentation with complaints consistent with BPPV is very common, the prevalence of undiagnosed BPPV is also high. In a prospective study in a community-based hospital located in a small Midwestern US city, 198 young adults (99 men and 99 women), aged 18–34 years, who were not being treated for dizziness or balance problems, were recruited [5]. Besides obtaining history and completing questionnaires, subjects underwent vestibular positional assessment for BPPV with infrared camera-equipped goggles recorded on digital media. The prevalence of BPPV in this young adult population was a surprising 9%. The rate of undiagnosed BPPV remains high throughout lifespan. Similar to the rate observed in the young adults, consecutive examinations of 100 older patients in an urban geriatric clinic revealed a 9% rate of undiagnosed BPPV [6]. The one-year prevalence of individuals with BPPV attacks (new-onset and recurrent) is believed to rise steeply with age: from 0.5% in 18- to 39-year olds to 3.4% in individuals over 60 years of age and the cumulative

(lifetime) incidence of BPPV reaches almost 10% by the age of 80 [2]. These statistics are very reproducible, for example, 11% of a large population of 75-year-olds manifested BPPV symptoms [7]. Women are two times more likely to suffer from BPPV [2]. Patients with BPPV are 5 times more likely to have relatives with BPPV compared to other dizzy patients suggesting a familial tendency [8].

Subjectively, the primary complaint at presentation is dizziness triggered by movement, such as looking up or on head turn. The intense sensation of vertigo triggered typically is short; however, patients feel off balance even when avoiding sudden head movements. Common characteristics of BPPV include rotational vertigo (in 86%), oscillopsia (31%), nausea (33%), vomiting (14%), imbalance (49%), fear of falling (36%), and falls (1%) [2]. As such, BPPV has adverse psychosocial consequences including reduced health-related quality of life [9], severe subjective impairment, and avoidance behavior in 70% of sufferers [10]. Patients with BPPV are more likely to have depression and reduced activities of daily living scores and sustained a fall in the previous 3 months [6]. High incidence in the geriatric population is of particular concern because they are already at risk (e.g., due to existing balance problems, osteoporosis, etc.) for morbidity (e.g., bone fractures) and mortality (e.g., skull fracture and/or intracranial hemorrhage, fat emboli form hip fractures) from falls. BPPV increases the risk of falls, especially in the geriatric patients [11]. Older patients (older than 70 years of age) with BPPV take longer to seek help and may present with complaints of unsteadiness or imbalance without vertigo sensation [12]. This was also found in a group of older patients referred to a Falls and Syncope Unit for evaluation who were eventually diagnosed with BPPV [13]. The reason for referral for evaluation of falls and syncope in this group of older, undiagnosed BPPV patients may be their less obvious and less characteristic presentation [13].

The economic burden of vertigo was evaluated using, in the 4,294 patients, multinational REVERT database which includes data from 618 centers [14]. Among those still employed, 69.8% had reduced their workload, 63.3% had lost working days, and 4.6% had changed their jobs. 5.7% had quit their jobs. In the 3 months preceding a visit, patients used emergency services 0.4 ± 0.9 times, primary care consultations 1.6 ± 1.8 times, and specialist consultations 1.4 ± 2.0 times (all mean $\pm$ SD). A mean of 2.0 ± 5.4 days/patient was also spent in hospital due to vertigo. Therefore, in addition to the negative impact on the patient from a humanistic perspective, vertigo, including BPPV, has considerable impact on work productivity and healthcare resource use. The costs of caring for BPPV are estimated to be more than $2,000 per individual, much of that arising from expenses associated with unnecessary diagnostic measures and ineffective therapy [15].

Reflecting the natural course of the disease, BPPV episodes are typically self-limited. Episodes of BPPV are mostly short with a median duration of 2 weeks, possibly accounting for why only 8% of all participants with BPPV received effective therapy [2]. In more than half of the patients, BPPV is a recurrent disease with a recurrence risk of approximately 15% per year [2]. The probability of recurrence is not different between the three semicircular canals [16]. In about 25% of recurrences, contralateral ear has been reported to be involved, leading to the suggestion that some systemic factors might facilitate otoconia detachment [16].

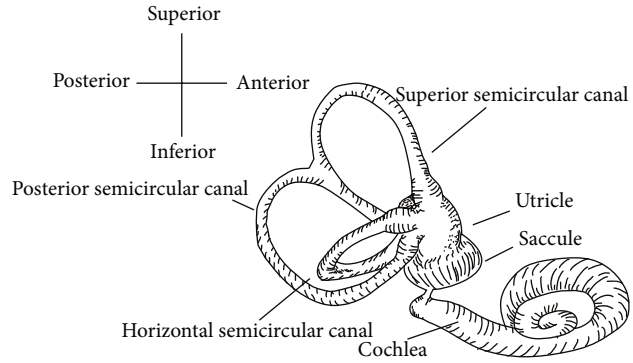

Figure 1: Schematic illustration of the inner ear composed of the cochlear and vestibular end organs. Structural relationship of the semicircular canals relative to one another and the utricle is demonstrated.

Despite the fact that BPPV is a relatively common condition, because the severity and nature of presenting complaints can vary, BPPV has a low recognition rate in the primary care setting [17]. The failure to correctly diagnose BPPV likely accounts for the poor referral patterns and low proportion of patients who receive appropriate symptom relief from the available treatments.

2. Applied Anatomy

The inner ear contributes to two senses: balance and hearing. It is the exclusive end organ for hearing which is served by the cochlea. The vestibular component of the inner ear is an important end organ for balance which in coordination with other inputs (i.e., proprioceptive and visual) to the brain subserves the sense of balance. The peripheral vestibular system consists of five distinct elements on each side: three semicircular canals and two otolithic organs, the saccule and the utricle (Figure 1). There are excellent reviews of peripheral vestibular anatomy and function available elsewhere [18, 19]. A brief overview is offered here to facilitate an appreciation of the pathophysiology of BPPV.

The inner ear membranous structures and epithelium are encased in the otic capsule which is one of the densest bones in the body. The otic capsule, located in the petrous portion of the temporal bone, unlike other bones in the body, has very little turnover, in part because of factors such as osteopontin in inner ear fluids that suppress bone remodeling [20]. The bony canal houses a membranous duct with the space in between being filled by perilymph. The fluid composition of perilymph is similar to that of cerebrospinal fluid. The membranous duct is filled with endolymph. Secretion of endolymph is localized to the stria vascularis in the cochlea and the dark cells in the vestibule. The ampulla of the semicircular canal secrete a potassium-rich, positively polarized fluid, the secretion of which is dependent on basolateral Na+,

K(+)-ATPase, and Na-K-Cl cotransporter [21]. The ampulla rests at one end of the bony/membranous canal and houses the crista ampullaris. The crista ampullaris includes sensory transducers (the hair cells) and the supporting structures, as well as a gelatinous fibrillar matrix, referred to as the cupula, in which stereocilia of the hair cells are embedded. The specific gravity of the cupula is similar to that of the endolymph. With rotation of the head, the endolymph filling the membranous ducts is displaced resulting in pushing or pulling of the cupula thus deflecting the stereocilia. Depending on the direction of the deflection and the ear in question (toward or away from the kinocilium), the hair cells can be stimulated or suppressed. The resulting signal is carried to the brain by the vestibular branch of the cranial nerve VIII which consists of bipolar afferents whose peripheral endings include large calyxes for faithful sensorineural synaptic transmission from the hair cells.

The three canals lie nearly perpendicular to each other and can code three planes (roll, pitch, and yaw) along the x-, y-, and z-axes [22]. Pitch plane corresponds to laying down, sitting up from supine position, or looking up- or downward, while movement along the roll plane corresponds to rotating the head toward the right or left in supine position [23]. Movement along the yaw plane is rotating head to the left or right in the sitting position. Therefore, the semicircular canals are best suited for detecting angular acceleration during rotational head movements. The kinocilium faces the utricle in the horizontal semicircular canal and faces away from the utricle for the posterior and superior semicircular canals. Deflection toward the kinocilium (utricopedal) results in excitation and away from the kinocilium (utricofugal) produces inhibition. The kinocilia of the crista ampullaris in the posterior and superior (anterior or vertical) semicircular ducts are oriented to depolarize the hair cells when endolymph moves in the utricofugal direction. Head turn to one direction in a given plane results in movement of the endolymph in the opposite direction. Each semicircular canal works in concert with the corresponding canal located on the other side of the head. They are both oriented in the same plane; however, hair cells would be expected to convey the opposite signal to the brain due to the opposite direction of endolymph/cupula displacement on head rotation.

The otolithic organs are best suited for detecting linear acceleration. They consist of the utricle and the saccule. Because of their orientation, which is orthogonal to one another, the utricle is more sensitive to linear acceleration and head movements in the horizontal plane, whereas the saccule is more sensitive to linear acceleration and head movements in the vertical plane. The saccule is in continuity with the cochlea through ductus reunions, thus has some low-frequency sound sensitivity. The utricle is more proximate to the semicircular canals which are in continuity with the vestibule, but appears to have some sound sensitivity as well [24]. Macula of the utricle and saccule house the sensory receptors, the hair cells. The sensory epithelium projects hair cells into an otoconial membrane (a viscous gel layer) on which the otoconia rest. The crystals get displaced during linear acceleration, which in turn deflects the ciliary bundles of the hair cells and thus alters the vestibular signal sent to the brain. Otoconia are calcite crystals composed of calcium carbonate [25]. They have a specific weight of 2.95 grams per cubic cm and are typically hexagonal in shape and 3 to 30 μm long (see below). Because of their mass, they permit sensitivity to gravitational forces.

Saccular function can be measured using vestibular evoked myogenic potentials (VEMP) [26, 27]. VEMP can help identify lesions along the pathway that connects the saccule via the inferior vestibular nerve and the descending vestibulospinal pathways to primarily the ipsilateral sternocleidomastoid muscle. The stimulus is a series of tone bursts and the evoked potentials are averaged to generate a waveform. Subjectively, dizziness with sensation of falling is typically associated with saccular dysfunction and VEMP abnormalities [28]. A variant of the cervical VEMP is a myogenic response that has been evoked around the eye (ocular VEMP) [29, 30]. In ocular VEMP, tone bursts delivered to one ear evoke myogenic potentials in the contralateral inferior oblique muscles with information being conveyed through afferent fibers travelling in the superior vestibular nerve. Clinically, applications of ocular VEMP are limited. However, in one study, abnormal function of the utricle was implied by abnormal ocular VEMPs recorded in BPPV patients [28].

3. Formation and Structure of Otoconia

Wang and colleagues were able to identify the principal organic component of the otoconia and partially sequenced and cloned the major protein component of murine otoconia, otoconin 90 [31]. Because of its similarity to secretory phospholipase A2 (sPLA2), this gene was referred to as PLA2-like (PLA2L) and enabled the identification of human otoconin 90. The rigid structure of sPLA2 is conveyed by six or seven disulfide bonds and is conserved in the otoconia and is essential for optimal interaction of the molecule with the mineral phase [32]. The molecular weight of otoconin 90 ranges between 90 and 100 kD, about half of which is accounted for by posttranslational modifications, consisting predominantly of sulfated glycosaminoglycans. Using a hyaluronidase-gold labeling technique, the localization of glucuronic acid-containing glycosaminoglycans in the gerbil utricle was examined by Tachibana and Morioka [33]. They observed that otoconia and the gelatinous layer of the otoconial membrane were strongly labeled by hyaluronidase-gold and secretory granules in supporting cells suggesting that the organic matrix of otoconia is secreted from these cells. The hyaluronidase labeling is lost as otoconia degenerate and are absorbed into dark cells.

Another protein, otolin, was described as the principal scaffold protein which was initially characterized in the zebra fish [34, 35]. Otolin is a short chain collagen with a highly interactive C1q globular domain. Subsequent work in mouse documented the mammalian ortholog of otolin [32, 36, 37]. Zhao and colleagues used gene targeting and protein analysis techniques to demonstrate that otoconin 90 is essential for formation of the organic matrix of otoconia by specifically recruiting other matrix components, which include otolin [38]. They demonstrated that this matrix controlled otoconia growth and morphology by embedding the crystallites during

seeding and growth. During otoconia development, the organic matrix forms prior to calcium carbonate ($CaCO_3$) deposition and provides optimal calcification efficiency. Yang and colleagues showed that matrix components are recruited to form the crystal matrix and sequester Ca(2+) for spatial specific formation of otoconia [36]. Specifically, they demonstrated that otoconin 90 binds otolin. In wild type mice otoconin 90 leads to an enrichment of Ca(2+) in the luminal matrices of the utricle and saccule, whereas absence of otoconin 90 in the null mice leads to significantly reduced matrix-Ca(2+). Both otoconin 90 and otolin were noted to increase the propensity of extracellular matrix to calcify in cell culture, but together they had a synergistic effect on calcification.

Andrade and colleagues used immunogold TEM to localize matrix proteins in mice [39]. They made several key observations. First, they demonstrated a high density of otoconin 90 in the inner core of otoconia, where they are arranged in oval patterns implying that otoconin 90 is attached to a scaffold consisting of the hexagonal fibrillar meshwork, characteristic of otolin. Second, the level of mineralization was much higher in the outer cortex where mineralized fiber bundles are arranged parallel to the surface. Based on this finding and observation from decalcification experiments, they concluded that otolin matrix fibrils serve as scaffold to guide mineralization mediated by otoconin 90. Third, they showed that individual crystallites assemble into iso-oriented columns and that the columns are arranged in parallel lamellae which convert into mineralized blocks for hierarchical assembly into the complex otoconial mosaic. Fourth, they demonstrated that in young mice the fibrils interconnecting otoconia consisted of the short chain collagen otolin. Fifth, they also observed that in old mice the superficial layer of mouse otoconia demineralized thus producing weakening or loss of anchoring of the organic fibrils interconnecting otoconia.

Using energy dispersive X-ray microanalysis and powder X-ray diffraction, otoconia have been described as calcite-based nanocomposites consisting of a relatively uniform outer shape with a cylindrical bulbous body (belly) and three rhombohedral, terminal planes at both ends which are part of its branches [40]. Degenerative changes can range from mild structural alteration such as fissures and surface roughening of the less dense belly area to fractures and disintegration leading to loss of otoconia [40]. The final component of the disintegrating otoconia that leads to fragment formation occurs in the belly [40]. These degenerative changes tended to increase with age. With age, the superficial layer of mouse otoconia becomes demineralized resulting in weakening or loss of anchoring of the fibrils interconnecting otoconia [39]. Consequently, otoconia can detach from each other and be released into the endolymphatic space by minor mechanical disturbances. The mechanisms leading to degeneration and eventual fragmentation of otoconia remain unknown.

Other mechanisms that could contribute to otoconia fragmentation include a change in endolymph such as change in pH, specifically acidic range, or calcium concentration. For example, EDTA exposure causes an anisotropic solubility of human otoconia, affecting the belly region [41]. Aminoglycosides such as gentamicin can also induce morphological changes in the structure of otoconia leading to eventual fragmentation and dissolution [41].

In summary, these results demonstrate that otoconia are composed of organic and inorganic components. The organic matrix is primarily composed of otoconin 90, around an otolin scaffold. The combination of these two components attracts and facilitates mineralization of calcium carbonate around the inorganic matrix to form calcite crystals. The otoconia are held anchored together with otolin-based fibrils. The structure of otoconia and the fibrils that hold them together is affected by the aging process and other disease processes, thus creating conditions under which otoconia can fragment and separate from the otoconial membrane.

4. Mechanisms of Disease

BPPV is believed to arise from displacement of particulate matter, likely fragments of otoconia from the utricle, into the semicircular canals. This idea was initially put forth by Schuknecht [42, 43] based on intricate insight in vestibular structure and function and histopathologic observations of basophilic staining masses of granular or homogeneous material found attached to the cupula of the posterior semicircular canal on the affected side. In a subsequent report, Schuknecht and Ruby reported finding copular deposits in 37% of temporal bone specimens and that 58% of these were located in the posterior canal [44]. Although the mechanisms leading to BPPV symptoms were a matter of long-standing debate [45], today, there is little doubt about the role of particulate matter. The involvement of particulate matter within the posterior semicircular canal has been established intraoperatively in patients with BPPV [46, 47]. Welling and colleagues prospectively examined the posterior semicircular canal of patients with and without a clinical history of BPPV for the presence of particulate matter. No particles were observed intraoperatively in any of the 73 patients undergoing labyrinthine surgery (vestibular schwannoma excision or labyrinthectomy) without a history of BPPV [48]. Particulate matter was observed in only 8 of 26 patients with intractable BPPV at the time of the posterior semicircular canal occlusion procedure. Similarly, Beyea and colleagues reported 20% incidence of free floating particles in the posterior semicircular canal of patients undergoing transmastoid posterior canal plugging for intractable BPPV [49]. However, particulate matter has also been reported in non-BPPV patients who underwent posterior canal fenestration carried out in patients undergoing acoustic tumor removal via a translabyrinthine approach [50]. Particles were identified in the membranous labyrinth in nine out of ten patients. However, only one of these patients described positional vertigo preoperatively. These observations suggest that mere presence of particulate matter is not sufficient and that there are other conditions that can influence the expression of disease symptoms.

Suzuki and colleagues created an in vitro experimental model by placing the posterior semicircular canal isolated from the frog in Ringer's solution. Saccular otoconia were used to stimulate the cupula [51]. Posterior semicircular canal

ampullary nerve action potentials instantaneously changed according to the direction of the gravity produced by otoconia. When the otoconia were dropped into the canal to mimic the condition of moving otoconia in the canal, the action potentials changed together with the otoconial flow after a latent period. They interpreted the findings as moving otoconia (i.e., canalolithiasis) with a latent period that better explain clinical features of BPPV. Using a similar approach Otsuka and colleagues used a whole membranous labyrinth of bullfrogs to replicate the human vestibule [52]. They exposed the posterior semicircular canals but left the remaining membranous labyrinth encapsulated in the otic capsule. They demonstrated that a vibratory stimulus (a surgical drill applied to the surface of the bony capsule) was able to detach the otoconia from the utricle, consistent with the view that mechanical insult could be a possible etiology of BPPV. They adjusted the position of the preparation so that the dislodged otoconia were attached to the cupular surface to model cupulolithiasis. Alternatively, when the otoconia were dislodged and held within the posterior semicircular canal lumen and the position of the whole preparation was changed so that the otoconia moved back and forth within the canal lumen, canalolithiasis was modeled. In the cupulolithiasis model, the vestibular nerve action potentials changed instantaneously according to the gravitational force on the cupula. In the canalolithiasis model, the action potentials changed in combination with the otoconial movement after a latent period. This experimental preparation has been used to model canalolithiasis and cupulolithiasis and recorded ampullary nerve discharges in the bullfrog [53]. In the canalolithiasis model, the acceleration of the otoconia was greater for the quick positional change. This resulted in a greater discharge with a longer duration. With the slow positional change, the discharges were smaller and shorter. In the cupulolithiasis model, the discharges were sustained and their magnitude did not differ between the quick and slow positional changes. The canalolithiasis model influenced the magnitude of discharge of the posterior semicircular canal depending on the speed of the positional change.

Rajguru and Rabbitt induced canalolithiasis in an animal model (oyster toadfish, *Opsanus tau*) by introducing heavy glass microbeads into the lumen of the lateral semicircular canal [54]. Bead movement under the action of gravity and canal afferent nerve discharge near the ampulla were recorded extracellularly in vivo. The magnitude and time course of the afferent responses explained the symptoms of BPPV. A single glass bead with a diameter of about 20 μm moving at nearly 80 μm/s within the lumen of the canal elicited pathological afferent inputs to the brain equivalent to an angular head velocity stimulus of about 100°/s. When the head was oriented nose-down, beads moved toward the nose and the lateral canal afferent discharge rate increased. Afferents that normally encoded angular velocity during oscillatory head rotations responded with tonic increases in the discharge rate during gravity-dependent bead movement. Other afferents, such as the units that rapidly adapt to a step increase in angular head velocity, responded with an initial increase in discharge rate followed by a period of adaptation. Afferent responses occurred in the complete absence of head movement and quantified the pathological inputs to the brain that arise from canalolithiasis.

Others have adopted a mathematical modeling approach to BPPV. Squires and colleagues utilized known hydrodynamic calculations and make reasonable geometric and physical approximations to derive an expression for the transcupular pressure ΔP_c exerted by a settling solid particle in canalolithiasis [55]. Based on this model, the authors came to several conclusions: (1) a pressure amplification occurs as otoconia enter a narrowing duct; (2) an average-sized otoconium requires approximately 5 seconds to settle through the wide ampulla, where ΔP_c is not amplified, which suggests a mechanism for the observed latency of BPPV; (3) an average-sized otoconium beginning below the center of the cupula can cause a volumetric cupular displacement on the order of 30 pL, with nystagmus of order 2°/s, which is approximately the threshold for sensation; and (4) larger cupular volume displacement and nystagmus could result from larger and/or multiple otoconia. This group also utilized their model to estimate dynamic cupular and endolymph displacements elicited during horizontal canal BPPV provocative diagnostic maneuvers and canalith repositioning procedures [56]. The activation latencies in response to a horizontal canal BPPV provocative diagnostic test were predicted to vary depending upon the initial location of the canalith debris (e.g., within the horizontal canal lumen versus in the ampulla). Results explained why the onset latency of ocular nystagmus evoked by the Dix-Hallpike provocative maneuver for posterior canal BPPV are typically longer than the latencies evoked by analogous tests for horizontal canal BPPV.

Obrist and colleagues used an in vitro model to test the canalolithiasis hypothesis [57]. They carefully scaled the physical and geometrical parameters to study the mechanics of BPPV on an enlarged model of a single semicircular canal with laser vibrometry and video particle tracking. Early results support the prevalent theories on the mechanisms of BPPV.

Zucca and colleagues hypothesized that spontaneous recovery in untreated BPPV patient (usually in 2–6 weeks) is mainly due to the fact that endolymph, owing to its low calcium content (20 microM), is able to dissolve otoconia [58]. They immersed frog saccular otoconia in normal endolymph (Ca2+ content 20 microM) and in Ca2+-rich endolymphatic fluids (up to 500 microM) over a 3-week period. They demonstrated that normal endolymph can dissolve otoconia very rapidly (in about 20 hours). When the endolymphatic Ca2+ content was increased (50 to 200 microM), otoconia dissolution time was slowed down (about 100 to 130 hours, resp.) and it completely stopped when the endolymphatic Ca2+ content was of 500 microM.

To summarize, based on clinical and experimental evidence, displaced fragments of otoconia into the semicircular canals are now widely accepted as the cause of BPPV symptoms. However, a critical mass appears to be needed to evoke clinical symptoms, as mere presence of fragments within the semicircular canal is not always sufficient to induce a change in vestibular nerve activity. Experimental models effectively simulate canalolithiasis and cupulolithiasis providing empirical evidence in support of prevalent hypothesis on

pathophysiology of BPPV. Concentration of calcium in the endolymph plays an important role in the rate of resorption of otoconia and may influence the duration of a BPPV episode.

5. Diagnosis of Cupulolithiasis and Canalolithiasis and Identifying the Affected Canal

Historical recognition of BPPV and use of provocative positioning techniques in its diagnosis had been a point of discussion. Lanska and Remler [45], based on an excellent review of the extant medical literature, noted that Bárány in 1921 was the first to describe BPPV in detail. They also credited Dix and Hallpike [59] as being the first to clearly describe both the currently used provocative positioning technique and the essential clinical manifestations of BPPV elicited by that technique. The Dix-Hallpike maneuver is now a standard component of the evaluation of the dizzy patient. When performing this procedure, the examiner stands to one side of the patient and rotates the patient's head 45 degrees to that side to align the ipsilateral posterior semicircular canal with the sagittal plane of the body. Next, the examiner moves the patient, whose eyes are open, from the seated to the supine test-ear-down position and then extends the patient's neck slightly so that the chin is pointed slightly upward. The latency, duration, and direction of nystagmus, if present, and the latency and duration of vertigo, if present, are noted. Each position should be maintained at least 30–45 seconds or until nystagmus resolves. If positive, rotary nystagmus toward the test ear is commonly observed, which is induced by the movement of free-floating debris within the affected canal (away from the cupula, inducing deflection of the cupula away from the vestibule). If no nystagmus is observed, or if observed once it resolves, the patient is seated upright and once again eyes are monitored for nystagmus which is once again documented as above. The procedure is repeated for the opposite ear. More recently, head shaking during the exam has been proposed to increase the diagnostic yield of the Dix-Hallpike exam [60]. Specifically, patients suspected of having posterior canal BPPV, but with negative Dix-Hallpike, are recommended to undergo head shaking Dix-Hallpike. This subgroup of patients is suspected of having a milder form of posterior canal BPPV (also see below for "subjective BPPV"). The side-lying test which also stimulates the posterior semicircular canal may be more suitable for older patients because the head and neck are fully supported by the examination table [7]. In this test, after seating the patient on the examination table, the head is turned 45° away from the involved ear then the patient lies on the side of the involved ear [61].

Lansk and Remler point out that "despite their important contributions, neither Bárány nor Dix and Hallpike understood the pathophysiology of BPPV nor did they appreciate that the positioning techniques they used actually demonstrated pathology in the semicircular canals rather than the utricle." They go on to attribute the modern understanding of the pathophysiology of BPPV to Schuknecht's proposal that the dysfunction resulted from the gravity-dependent movement of loose or fixed dense material within the posterior semicircular canal ("cupulolithiasis") [42]. They add that although Schuknecht's formulations were not consistent with all clinical features of the disease, they led to the modern "canalolithiasis theory" and highly effective canalith repositioning or liberatory maneuvers for BPPV. Hall and colleagues brought clarity to understanding the mechanisms underlying posterior canal BPPV by emphasizing the importance of fatigability of symptoms [62]. Hall and colleagues noted that, under the influence of gravity, a density differential between the endolymph and the cupula will cause displacement of the cupula when changes in head position occur. They explained that BPPV can be divided into two types based on the presence or absence of fatigability. Specifically, nonfatigable nystagmus was the result of particles being fixed on the cupula (cupulolithiasis), whereas fatigable nystagmus was due to free floating particles within the body of posterior semicircular canal. This latter condition was subsequently referred to as canalolithiasis [63].

Theoretically, if particulate matter can be located in the long arm of the semicircular canals or attached to the cupula, distally, it could also be present in the short arm or attached to the cupula, proximally. Indeed a histopathologic study reported that canaliths have been found to be located in the short arm of the semicircular canals (proximate to the utricle) [64]. Clinical correlate of this entity has yet to be defined.

Posterior canal BPPV is the most common. In a study of 614 BPPV patients over an 11-year period, the posterior semicircular canal was affected in 543 cases (88.4%), the horizontal in 39 (6.4%), and the superior canal in 32 (5.2%) [16].

BPPV of the posterior canal, the most inferior canal, is believed to be much more frequent because gravitational forces settle the particles in this canal, particularly when the patient is in the lateral supine position [65]. In contrast, the superior semicircular canal is the highest point of the labyrinth, thus it is rarely involved in BPPV. To settle particles into the superior canal, very marked hyperextension of the head is required [65].

Several authors have characterized horizontal BPPV [66, 67]. Horizontal BPPV is triggered when the head of the supine patient is turned from side to side and is characterized by a bidirectional horizontal nystagmus. As with posterior BPPV there are also two subtypes of horizontal BPPV depending on the location of the otoconia fragments. In canalolithiasis, fragments of otoconia move freely in the horizontal semicircular canal inducing stimulatory utriculopetal endolymph flow, whereas in cupulolithiasisotoconia are attached to the cupula or are trapped in the proximal segment of the canal near to the cupula. In canalolithiasis, vertigo is triggered by circular acceleration in the plane of the horizontal semicircular canal while, in cupulolithiasis, vertigo is triggered when the head changes position, but not by circular acceleration. In canalolithiasis, nystagmus is geotropic (toward the undermost ear) and more intense after rotation of the head toward the affected side. In cupulolithiasis, the nystagmus during cupulolithiasis of the horizontal semicircular canal is apogeotropic (away from the undermost

ear) and more intense after rotation of the head toward the unaffected ear. It is recommended that, for patients presenting with symptoms of BPPV, if the Dix-Hallpike test is negative, a supine roll test be performed to assess for lateral canal BPPV [68].

Clinically identifying the affected side in horizontal canal BPPV can be challenging. The problem is that during diagnostic maneuver (e.g., the supine head roll test, also known as the Pagnini-McClure maneuver), one horizontal canal cannot be isolated from the other, as both head positions stimulate the horizontal canals resulting in nystagmus with either ear down. In addition, horizontal canal BPPV causes direction-changing nystagmus. As noted above, horizontal BPPV-related nystagmus can be geotropic or apogeotropic, but the direction of the nystagmus relative to the ground is the same in both positions of the supine head roll test. Ewald's second law provides guidance on determining the affected side. Ewald's three laws were generated after experiments in pigeons whose semicircular canals were stimulated using pneumatic devices [69]. They state that a stimulation of the semicircular canal causes a movement of the eyes in the plane of the stimulated canal. In the horizontal semicircular canals, an ampullopetal endolymph movement causes a greater stimulation than an ampullofugal one. In the vertical semicircular canals, the reverse is true. Ewald's second law has profound clinical implications. The directional asymmetry implies that, in persons who have lost inner ear function on one side, the remaining side should produce higher velocity nystagmus when the head is being rotated towards the remaining intact ear (ampullopetal), but less when the head is being rotated towards the side of vestibular loss. Aron and Bance provided validation of Ewald's second law in a rare case combining horizontal canal BPPV with a dead ear on the contralateral side, therefore arising from a known side [70]. They presented the case of an 87-year-old male with history of invasive left ear cholesteatoma which had fistulized into the horizontal canal. He underwent successful resection of disease with postoperative caloric testing showing absent responses on the left side and a "dead" ear. Ten years later, the patient presented with chronic dysequilibrium aggravated by head movements. Dix-Hallpike test was negative, but a supine head roll test demonstrated bilateral apogeotropic, horizontal nystagmus, which was more pronounced with the head turned to the left. Videonystagmography demonstrated the increased slow phase velocity of the nystagmus when the head was turned to the left (i.e., away from the affected ear). This case corroborates Ewald's law for lateralization of apogeotropic horizontal canal BPPV.

Patients with lateral canal BPPV may also exhibit a mild "spontaneous" horizontal nystagmus while in the sitting position but because presentation of nystagmus is strongly influenced by head position and movements, this type of nystagmus may be more accurately referred to as pseudospontaneous nystagmus [71]. It beats toward the healthy side when the lateral canal BPPV is geotropic and toward the affected side when it is apogeotropic and when absent [71, 72]; it is sometimes possible to evoke it with a mild shaking of the head [71]. Patients with apogeotropic show predominantly contralesional head-shaking nystagmus, whereas patients with geotropic type do not show any directional preponderance [72].

The "bow and lean test" has been promoted as a useful method to identify the affected side in horizontal canal BPPV [73]. In a prospective study, for diagnostic purposes, subjects were divided into two groups: standard head roll test versus the bow and lean test. The latter group had better remission rates for both canalolithiasis and cupulolithiasis of the lateral canal.

Initial presenting history can be an important aid in identification of the involved canal. There is a relationship between the position that initially provoked vertigo and the affected semicircular canal in patients with BPPV. History taking regarding the side of provoking position at the onset of vertigo helps predict the side affected by BPPV in both posterior canal BPPV and geotropic horizontal canal BPPV [23]. Although the type of BPPV cannot be predicted by the initial position provoking vertigo, the side of the BPPV is strongly correlated to the head-turning side in the supine position that initially provide vertigo in this group of patients.

When apogeotropic horizontal canal BPPV is suspected, further detailed examinations using additional localization methods, including supine head roll test and pitch-plane test, are typically needed. The waking-up position was the most common situation that initially provoked vertigo in all subtypes of BPPV, including geotropic and apogeotropic horizontal canal BPPV [23].

Until recently diagnosing of superior (anterior) semicircular canal BPPV was controversial. Because of its anatomical location, the superior semicircular canal is rarely affected in BPPV. In a retrospective study where over a 1-year period 4,320 patients consulting for otoneurological disease were investigated by otological, videonystagmography, and neurological examination, BPPV was diagnosed in 1,430 patients (33%) [65]. Among these the posterior semicircular canal was involved in 1,325 patients (92.6%), the horizontal semicircular canal in 85 patients (5.9%), the posterior semicircular canal and ipsilateral superior semicircular canal in 19 patients (0.01%), and the superior semicircular canal only in one patient (0.0007%). In the 20 patients with superior semicircular canal BPPV, the Dix-Hallpike test induced apogeotropic horizontal torsional nystagmus beating towards the uppermost ear in the lateral supine position with reversal on standing. That is nystagmus beating towards the uppermost ear on the Dix-Hallpike test is consistent with BPPV involving the superior semicircular canal of the uppermost ear. The author suggests that the torsional component of nystagmus and not just the vertical component must be taken into account to facilitate the diagnosis.

Multiple canals can be involved at presentation, not uncommonly after head trauma [74]. Involvement of multiple canals can give rise to atypical presentation and challenging management with repositioning maneuvers [74, 75]. It has been argued that the most significant factor in diagnosis of the type of BPPV is observation of the characteristics of the provoked nystagmus during the diagnostic positional maneuvers, although the combination of posterior-anterior canal involvement remains particularly challenging [76].

Special considerations are warranted in the geriatric population, because geriatric patients with BPPV usually report dizziness or imbalance and do not always describe a rotatory crisis. Batuecas-Caletrio and colleagues have argued that the Dix-Hallpike and supine roll tests should be performed in older patients with dizziness, despite the fact that they do not complain of spinning sensation with positional changes [12].

Finally, a number of studies have reported that the right ear is predominantly affected [10, 12, 16]. It has been suggested that prolonged lying may facilitate the deposition of otoconia on the cupula or contribute to their loosening from the utricle (see below) and that this mechanism might also explain why the laterality of BPPV often corresponds to the preferred side of lying during sleep [77].

6. Treatment

Mechanical repositioning: historically, as the proposed mechanism involving cupulolithiasis and canalolithiasis became more widely accepted, the idea of using head positioning maneuvers to relieve symptoms of BPPV evolved as an alternative to conservative management (i.e., avoidance of provocative head positions and changes) and surgical procedures. Brandt and Daroff used a physical therapy approach involving repeated maneuvers to loosen and disperse the degenerated otolithic material from the cupula [78]. These efforts were followed by liberatory maneuver of Semont [79] and subsequently canalith repositioning procedure of Epley (Figure 2) [80, 81]. Given that the dominant view at that time was that BPPV arose from the involvement of the posterior semicircular canal, these repositioning procedures were mainly directed at providing relief of posterior canal BPPV. However, several varieties of BPPV can be experienced depending on the semicircular canal involved, whether or not cupula is involved, single or multiple canal involvement, and sidedness of the affected structures. In fact, the effectiveness of the repositioning maneuvers varies depending on correct identification of the affected canal.

To assess the effectiveness of the Epley maneuver in treatment of posterior semicircular canal BPPV, Hilton and Pinder, in a Cochrane review, compared Epley maneuver versus placebo Epley maneuver versus untreated controls [82]. They evaluated the frequency and severity of attacks of vertigo, proportion of patients improved by each intervention, and conversion of a "positive" Dix-Hallpike test to a "negative" Dix-Hallpike test. Fifteen randomized trials were identified but twelve studies were excluded because of a high risk of bias, leaving three trials in the review. Trials were mainly excluded because of inadequate concealment during randomization, or failure to blind outcome assessors. The studies included in the review addressed the efficacy of the Epley maneuver against a sham maneuver or control group. They concluded that the Epley maneuver is a safe effective treatment for posterior canal BPPV. A more recent review 83 arrived at the same conclusion, noting that based on a systematic review of all relevant randomized controlled trials (Level I evidence) there is strong evidence of efficacy of the Epley maneuver in treatment of posterior canal BPPV, with no serious adverse effects.

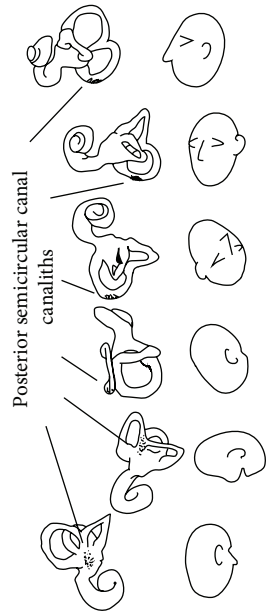

Figure 2: Illustration of the Epley maneuver for the treatment of left posterior canal BPPV. From a seated position (top), the patient's head is turned 45° to the left (2nd from top). The patient is laid down with the head rotated to the left and neck is extended (3rd from top). Next, the head is turned 90° to the right (4th from top) followed by rolling the body to the right such that patient is lying on the right shoulder looking toward the floor (2nd from bottom). Finally, the patient is returned to the seated position with head remaining rotated to the right (bottom). Each position is held for at least 30–60 seconds or until nystagmus or vertigo has resolved. Frenzel lenses can facilitate visualization of nystagmus. Adapted from Mitka [151].

There are currently two practice guidelines that are available for diagnosis and management of BPPV, one by the American Academy of Neurology [83] and another by American Academy of Otolaryngology-Head & Neck Surgery [68]. They both offer thorough reviews of the available evidence and validate the effectiveness of the Epley maneuver in management of posterior semicircular canal BPPV.

A more recent Cochrane review compared a modification of Epley maneuver to the standard Epley maneuver [84]. Nine studies included post-Epley postural restrictions. Such restrictions could include using a neck brace, head movement restrictions (avoiding bending the head up and down or bending over), and instructions to sleeping upright. The review concluded that there was a statistically significant advantage of post-Epley postural restrictions. Specifically, it was found that in the experimental group 88.7% versus 78.2% in the control group converted from a positive to negative Dix-Hallpike test.

The same Cochrane review found that there is insufficient evidence to support the routine application of mastoid oscillation during the Epley maneuver. Mastoid oscillation involves applying vibration to the mastoid bone behind the ear during the maneuver (an "augmented" Epley).

In a prospective study in geriatric BPPV patients, both clinical and functional aspects of body balance, including

postural instability, improved after treatment with the modified Epley maneuver [85]. However, in the older patients, the effectiveness of therapeutic repositioning maneuver (see below) is lower than those under 70 and the recurrences are more frequent [5].

At present, the best available treatment of the horizontal canal BPPV is the roll (Barbecue or Lempert) maneuver [67, 86–89]. The procedure is effective in managing lateral canal BPPV in a lower proportion of patients than Epley maneuver is in control of posterior canal BPPV (<75% versus 88%, resp.). The Gufoni maneuver is another technique that has been reported as effective in treating horizontal canal BPPV. In a double-blind randomized controlled trial, this maneuver proved effective for both geotropic and apogeotropic forms with 84% relief of vertigo after 24 hrs [90].

Options in management of the cupulolithiasis of the horizontal semicircular canal are very limited where the challenge is to detach the otoconia fragments from the cupula. It has been suggested that repetitive somersaults may be beneficial. In somersaults, acceleration in the forward-facing direction may induce an intracanalicular force strong enough to detach otoconia debris from the cupula and the ongoing rolling may move loose otoconia debris back into the utricle [91]. Yamanaka and colleagues described the head-tilt hopping exercise in treatment of cupulolithiasis associated with BPPV of the horizontal semicircular canal, which is characterized by apogeotropic direction-changing nystagmus [92]. This treatment is designed to release otoconial debris adherent to the cupula as the patients hopped while tilting their heads laterally. The treatment required several sessions daily over a 4-week period. Nystagmus of 33.3% patients with intractable lateral canal BPPV disappeared immediately after the first training session and after 1 and 4 weeks of the training, 56% and 70% of patients that had experienced improvements, respectively. It is important to note, however, given the natural history of BPPV, that absence of untreated control group significantly weakened the potential for generalization of this study.

In a recent study of 965 BPPV patients, canalith repositioning procedures (Epley and Barbeque maneuvers) provided long-lasting noninvasive treatment for BPPV with 85% effectiveness after the first procedure [89]. Fourteen percent of patients had recurrences, with this group of patients having characteristics of being older or having history of head trauma or vestibular neuropathy. The authors suggested that geriatric patients, because of a significantly higher recurrence rate, should have additional education to minimize potential morbidity of their falls.

In general, The Epley maneuver is effective in treatment of superior semicircular canal in 94.1% of cases after one treatment and 97.5% after multiple treatments [65]. However, in another report, therapeutic maneuvers were found to be more effective in resolving posterior canal or horizontal canal BPPV than superior canal BPPV [16]. Specific maneuvers for relief of superior canal BPPV have been described [93, 94]. For example, a sequence of maneuvers consisting of head positioning beginning supine with head hanging 30 degrees dependent with respect to the body, then supine with head inclined 30 degrees forward, and ending sitting with head 30 degrees forward are reported to relieve 100% of vertigo and nystagmus in one retrospective series [93].

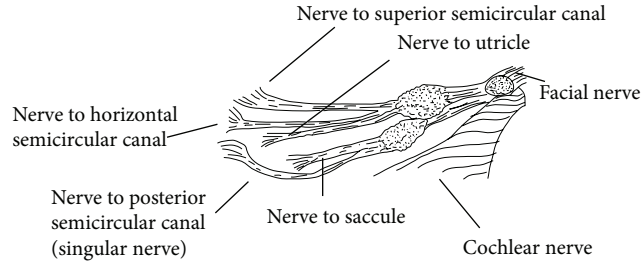

Figure 3: Schematic illustration of the nerves travelling through the internal auditory canal, including branches of the eighth cranial to the vestibular end organs. Singular nerve innervates the ampulla of the posterior semicircular canal.

Canalith repositioning, in an appropriately selected patient, is a generally safe procedure. Minor adverse events of canalith repositioning include severe nausea and vertigo during the procedure and instability or light-headedness for approximately 48 hours after the procedure [89]. Other complications have also been reported. The most common complication is canal switching, where otoliths from one semicircular canal are unintentionally displaced into another. Canal switching has been reported in 6% of the patients with posterior canal BPPV [95]. Canal switching appears to more likely during Epley than Semont maneuver because of the higher number of maneuver steps during which the head is in the dependent position [96]. A very rare and unusual complication is internal carotid artery dissection, with only one reported case [97].

Despite the effectiveness of the Epley maneuver to treat BPPV, it remains underutilized in many settings to which sufferers initially present, such as the emergency room [98].

Surgical management: surgical options are pursued when debilitating posterior canal BPPV is unresponsive to bedside repositioning. Posterior ampullary (singular) nerve transaction was the first proposed surgical treatment for intractable posterior canal BPPV [99]. Gacek was motivated by Schuknecht's observations of otoconial mass embedded in the cupula of the posterior canal crista (see above) which is innervated by the posterior ampullary branch of the inferior vestibular nerve (Figure 3). Gacek proposed singular neurectomy through a tympanotomy approach under local anesthesia for treatment of disabling chronic (greater than 1 year) BPPV [100].

Posterior semicircular canal occlusion (canal plugging) was first described by Parnes and McClure [47]. This operation can be effectively performed using a transmastoid approach [49]. Plugging is performed with bone dust mixed with fibrinogen sealant (bone pate) which is gently packed into a fenestration drilled into the posterior semicircular canal. In one series, all but one of 44 patients who underwent this procedure were relieved of BPPV on follow-up between 6 months and 12 years [101]. This treatment produces temporary postoperative imbalance and motion sensitivity for several weeks, but spares hearing.

7. Etiology

Soto-Varela and colleagues reported that the origin of BPPV remained unknown in 61.9%, but in the remainder, BPPV appeared to be associated with previous trauma (6.7% of all patients), ipsilateral Ménière's disease (6.5%), ipsilateral vestibular neuritis (5.6%), history of BPPV affecting the same ear (5.2%), a severe systemic disease (4.6%), and history otologic surgery (1%) [16]. Severe systemic disease included patients with carcinoma who were receiving treatment with radiotherapy or chemotherapy, recent myocardial infarction, leukemias treated with chemotherapy, sarcoidosis, and active ulcerative colitis.

Head trauma is a long recognized cause of BPPV [102]. Traumatic BPPV is more likely to be bilateral, occurring in 25% compared with only 2% in idiopathic BPPV [103]. A variant of posttraumatic BPPV is postsurgical BPPV. Among nearly 1000 cases, the incidence of BPPV after surgical drilling of the temporal bone was around 1%, and the horizontal semicircular canal of the contralateral ear was predominantly involved (90%) [104]. Maxillofacial (orthognathic) surgery has been reported to result in BPPV which can be bilateral and incapacitating occurrence which resolves slowly [105, 106]. Another example is rhinoplasty, possibly due to utilization osteotomies [107]. In comparing management of posttraumatic BPPV with idiopathic vertigo, it appears that typically more positioning maneuvers are needed to achieve relief in the former [108, 109].

Physical activity can also influence occurrence of BPPV independent of any specific trauma. Physical activity such as swimming [110] and mountain biking [111] have also been reported to trigger BPPV. On the other hand, prolonged bed rest has been recognized for a long time as a provoking factor for BPPV. It was suggested that prolonged lying may facilitate the deposition of otoconia on the cupula or contribute to their loosening from the utricle [112]. The above mechanism might also explain why the laterality of BPPV often corresponds to the preferred side of lying during sleep [77]. Consequently, it has been hypothesized that mild to moderate physical activity might relocate the particles from the canal, thus preventing the accumulation of an adequate number of otoconia necessary for forming an agglomerate [113]. Authors quantified physical activity during leisure, household, and occupational activities over a 7-day period in a group of 63 BPPV and 63 age- and gender-matched subjects. Physical activity was significantly lower in patients with idiopathic BPPV than in controls regardless of gender and occupational activity. The difference was mainly in individuals older than 60 years. Most of the individuals at this age are retired, which explains why leisure and household activities may become more important. While geriatric patients did not differ from controls in occupational activity, they demonstrated less daily leisure and household activity than controls. Finally, trauma can also be without a direct physical component. For example, radiation therapy for treatment of nasopharyngeal carcinoma has been reported to induce BPPV [114]. Other unusual causes include occlusion of the anterior vestibular artery causing a sudden vertigo crisis (Lindsay-Hemenway syndrome) that includes otolith disease [115].

Given that BPPV affects a substantial proportion of the population and that there remain significant limitations in our ability to fully control its symptoms and recurrences, over the past decade effort has been directed at identification of medical factors that may predispose a patient to development of idiopathic BPPV. Associations have been reported between BPPV and diabetes [116]. In a case-control histopathologic human temporal bone study, temporal bones from patients with type 1 diabetes mellitus and normal temporal bones from age-matched individuals were histopathologically examined [117]. It was found that the prevalence of cupular and free-floating deposits in the lateral and posterior semicircular canals was significantly higher in type 1 diabetes mellitus patients compared with normal temporal bones. Another systemic link was described recently where the lipid profiles and serum uric acid levels were found to be higher in patients with BPPV than in controls [118]. Curiously, serum uric acid levels decreased one month after the BPPV attack; however, the mechanisms behind these observations have not yet been elucidated. Other conditions that have been associated with BPPV include chronic thyroiditis [119], hypertension, hyperlipidemia, and stroke [2].

To find a statistical link between common comorbidities affecting the elderly population (hypertension, diabetes, osteoarthrosis, osteoporosis, and depression) and recurrent episodes of BPPV data from over 1,000 BPPV patients in 11 centers across 7 countries were examined [120]. The results showed the presence of at least one comorbid disorder in 20% of subjects and 2 or more in 37% of subjects. Furthermore, it was noted that over 50% of subjects had at least one recurrence and that the higher the number of comorbidities, the greater the number of recurrences.

Among the comorbidities, the association with osteoporosis has raised much interest, in part because it implies that abnormal bone turnover may underlie BPPV. Vibert and colleagues reported that among thirty-two 50–85-year-old Swiss women with idiopathic BPPV, 75% had osteopenia/osteoporosis on dual X-ray absorptiometry (DEXA) [121]. Jang and Kang reported that Korean women (20–69 years of age) with idiopathic BPPV had lower bone mass density (BMD) values compared to "normal" controls [122]. They also reported that patients with low BMD measured by DEXA had increased recurrence rate and required an increased number of canalith repositioning maneuvers. Jeong and colleagues evaluated BMD of 209 Korean men and women with idiopathic BPPV and compared them to control subjects without history of vertigo. The prevalence of osteopenia and osteoporosis was higher in both women and men with BPPV than in controls [123]. Mikulec and colleagues conducted a retrospective chart review to assess the prevalence of "treated osteoporosis" (on antiresorptive therapy) in 260 women with and without BPPV between 51 and 80 years of age [124]. They observed a statistically significant negative association between BPPV and "treated osteoporosis" in women aged 51–60 years but not the older group. Among Japanese BPPV patients with osteoporosis, the incidence of recurrence was 56.3% (compared to 16.1% in those with normal bone mineral density) and the frequency of BPPV recurrence increased as BMD decreased [125]. Finally, Korean patients with BPPV

show a higher prevalence of vitamin D deficiency [126] and a recent pilot study showed that in 4 Austrian patients with BPPV recurrence, vitamin D levels were lower than those without recurrence and recurrences were relieved with vitamin D supplementation [127].

Although these studies have investigated the association between BPPV and low bone mineral density, the cooccurrence of two morbidities is not by itself supportive of causation. Low bone mineral density (e.g., in premenopausal women) might reflect low peak bone mass based on genetic predisposition, environment, and lifestyle factors [128] and osteopenia/osteoporosis are prevalent disorders of aging. Furthermore, a limitation of asserting an association based on DEXA scan findings is that any physiological alterations in bone turnover take about one year to be detectable by DEXA scan [129]. Since osteoporosis is a slowly changing disease process there is an obvious incongruence between DEXA scan findings and BPPV episodes, which tend to present abruptly and typically are self-limited (days to weeks in duration). An alternative approach is to examine biochemical markers of bone turnover, whose levels change rapidly (within 1–3 months) and are more temporally relevant to the natural history of BPPV. Parham and colleagues used these markers to demonstrate that idiopathic BPPV patients tend to have higher levels of biochemical markers of bone turnover and that these levels are influenced by vitamin D level [130].

8. Differential Diagnosis

Although BPPV is one of the most common causes of vertigo, it is not the only disorder associated with recurrent vertigo. Meniere's disease, migraines, vertebrobasilar insufficiency, and panic disorder are also characterized by recurrent episodes. Caution in diagnosis BPPV is warranted as other conditions can present with BPPV-like symptoms. For example, central vestibular disorders can give rise to positional nystagmus, which can be mistaken for BPPV. Such lesions can arise from posterior fossa such as from small cerebellar strokes [131]. In inner ear pathologies which may cause vestibulopathies, such as perilymph fistulas, nystagmus may be enhanced by Dix-Hallpike testing. Furthermore, as spontaneous nystagmus associated with a perilymph fistula improves, nystagmus toward the affected ear in the downward position may misdirect the examiner from the initial pathological trigger of the symptoms. Other vestibulopathies that cause horizontal nystagmus may also be enhanced by Dix-Hallpike testing. Welgampola and colleagues cite another example where spontaneous horizontal nystagmus from acute peripheral vestibulopathies may be enhanced by Dix-Hallpike testing [132]. Specifically, spontaneous nystagmus from a right-sided vestibular neuritis will be left beating in the left lateral and right lateral positions. In contrast, nystagmus from left horizontal canal BPPV will be vigorously left beating in the left lateral position and will beat less vigorously to the right in the right lateral position. Low-velocity sustained horizontal, vertical, or torsional nystagmus can be found in patients with clinically definite vestibular migraine [133]. BPPV occurs more frequently in patients with migraines than those without [134]. One study reported that migraines were 3 times more likely in BPPV patients than in general population and a family history of migraine is present in nearly 60% of BPPV patients [135]. Prevalence of migraine in patients that have been diagnosed with BPPV of childhood is higher than in the general population, which led to the proposal that childhood BPPV is a precursor of migraine [136].

BPPV can occur secondary to various other conditions including viral neurolabyrinthitis, Meniere's disease, and vertebrobasilar ischemia [137]. In Meniere's disease, it has been suggested that hydropic distension or rupture damages the otolithic apparatus, leading to the release of otoconia debris which migrate to the semicircular canals where they may result in BPPV [138]. Balatsouras and colleagues reported that the BPPV associated with Meniere's disease differs from idiopathic BPPV in regard to several epidemiological and clinical features, may follow a different course, and responds less effectively to treatment [139]. In a retrospective/epidemiological study of 345 BPPV patients, they identified 8.4% incidence of Meniere's disease. The patients with BPPV associated with Meniere's disease tended to be greater than 90% female, have had a longer duration of symptoms, commonly had involvement of the horizontal semicircular canal (25%), had a greater incidence of canal paresis on videonystagmography, needed more therapeutic sessions to relieve their BPPV, and had a higher rate of recurrence.

Lee and colleagues reported that BPPV may occur secondary to inner ear diseases, including idiopathic sudden sensorineural hearing loss (51%), Meniere's disease 28.9%) and unilateral vestibulopathy such as acute vestibular neuronitis and herpes zoster oticus (20.2%) [140]. They further noted that Meniere's associated BPPV most commonly involved the lateral canal. The durations of treatment for idiopathic BPPV and BPPV secondary to inner ear diseases were 2.28 and 4.87 days, respectively. The mean duration of treatment was 6.28 days for idiopathic sudden sensorineural hearing loss with BPPV, 5.07 days for BPPV with unilateral vestibulopathy, and 2.28 days for BPPV with Meniere's disease. Of note, BPPV in idiopathic sudden sensorineural hearing loss patients portends a poor prognosis [141].

There appears to be a variant condition where recurrent vertigo associated with fast head movements and history consistent with BPPV is associated with absence of nystagmus on the Dix-Hallpike maneuver [139, 142–145]. This variant is known as "subjective BPPV" [139] or "sitting-up or Type 2 BPPV" [145]. It is characterized by vertigo and/or nausea in the absence of nystagmus during the Dix-Hallpike or roll test. Alvarenga and colleagues suggested that the patients could have small amounts of calcium carbonate particles stuck to the cupula or floating in the affected semicircular canal which may not be enough to cause nystagmus, but sufficient enough to induce nausea and/or vertigo [144]. Others suggest that this condition may be related to chronic canalolithiasis within the short arm of a posterior canal [145]. An alternate explanation was put forward when Johkura and colleagues noted that nystagmus may be present but may be too subtle to detect without additional instrumentation [146]. They investigated 200 geriatric patients with dizziness with an infrared camera and video-oculography and found a faint

positional apogeotropic horizontal nystagmus, compatible with horizontal semicircular canal BPPV in nearly 50% of the patients. This nystagmus was not detectable with Frenzel glasses. Gans has offered a fourth explanation based on a change in the calcium metabolism and the consequent nonabsorption of free otoliths [147], which would increase their quantity in the semicircular canals and enable the triggering of vertigo upon head movement. Alvarenga and colleagues suggest that the affected labyrinth can be identified based on which side induced nausea or vertigo on positioning testing [144].

Regardless of etiology, BPPV arising from other inner ear diseases [140, 148] and subjective BPPV [149] can be treated using the same approach as to typical BPPV, although success rate may be slightly lower. Finally, intracranial tumors can cause positional vertigo which should be differentiated from BPPV based on history and neurotological examination findings [150]. The differentiating features include symptoms duration >35 days, sensorineural hearing loss, nonfatiguability positional nystagmus, variable duration and latency of nystagmus on positional changes, nonresponsiveness to canalith repositioning, and possible rollover phenomenon. This latter entity has been referred to as malignant paroxysmal positional vertigo [150].

9. Summary and Future Directions

BPPV is believed to be a focal disorder of the inner ear with manifestations which affect the well-being and functional capacity of the sufferers. It occurs more frequently in women than men (2 to 1 ratio) and its prevalence increases with age. BPPV arises from displacement of otoconia fragments into the semicircular; however, a critical mass is needed to evoke clinical symptoms, as mere presence of fragments within the semicircular canal is not always sufficient to induce a change in vestibular nerve activity. Because of the anatomy of the inner ear, the posterior semicircular canal is more commonly affected, but lateral and superior canals can also be involved. In the majority ofcases, diagnostic maneuvers, such as the Dix-Hallpike and head roll test, can effectively lead to identification of the involved canal, although diagnosing the affected side in lateral canal BPPV can be challenging. Otoconia are composed of organic and inorganic components. The organic matrix is primarily composed of otoconin 90, around an otolin scaffold. The combination of these two components attracts and facilitates mineralization of calcium carbonate around the inorganic matrix to form calcite crystals. The otoconia are held anchored together with otolin-based fibrils. The structure of otoconia and the fibrils that hold them together is affected by the aging process and other disease process.

The natural history of BPPV is one of a self-limited disease in which symptoms resolve as otoconia fragments dissolve into endolymph. The rate of dissolution of the fragments is dependent on calcium concentration within the endolymph, such that low concentrations lead to faster resolution. Canalith repositioning maneuvers effectively manage the majority of cases. Evidence supports treatment of the posterior canal with the Epley maneuver, which also appears to be effective in management of the superior canal BPPV. The Lempert or Gufoni maneuvers can effectively manage lateral canal BPPV, assuming the affected side has been correctly identified.

The majority of BPPV cases are idiopathic; however, other inner ear diseases (e.g., labyrinthitis, Meniere's disease) and head trauma (e.g., accidental or intraoperative/iatrogenic) can lead to BPPV. Idiopathic BPPV may be closely associated with systemic diseases such as diabetes and osteoporosis. A predisposition to developing BPPV is supported by the high rate of idiopathic disease, recurrences months after resolution, recurrences that can be in contralateral ear, and a familial tendency for the occurrence of BPPV.

Further investigation of systemic causes of idiopathic BPPV may introduce a major shift in the clinical management paradigm for BPPV. Currently, the dominant clinical perception of idiopathic BPPV is that of a purely otologic disorder and, therefore, management is focused on canalith repositioning only. With identification of the clinical variables that contribute to idiopathic BPPV or increase vulnerability to development of BPPV, clinical management of BPPV will likely evolve beyond treatment of acute episodes with canalith repositioning to global management aimed at preventing the disease and its recurrences.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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