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Review

Benign Paroxysmal Positional Vertigo: Is It Really an Otolith Disease?

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The current theory in physiopathology of benign paroxysmal positional vertigo is the mechanical theory, namely the cupulolithiasis–canalolithiasis theory. Repositioning maneuvers based on this theory has now taken place in therapy. However, mechanical theory is insufficient to explain some clinical situations and cannot fully enlighten the physiopathology. Mechanical theory is based on very few histological studies. Currently, these few articles are still used for reference. Anatomically, there are uncertainties that need to be explained in this theory. In this literature review, the histological and anatomical evidence is reviewed and the value of mechanical theory in benign paroxysmal positional vertigo physiopathology has been questioned. Studies suggest that the debris in the semicircular canals is caused by degeneration due to aging and may not be responsible for the symptoms in benign paroxysmal positional vertigo. Some patients with debris in semicircular canals do not have benign paroxysmal positional vertigo symptomatology, while some patients without debris may have benign paroxysmal positional vertigo symptomatology. Experimental and histological findings suggest that vestibulopathy due to inflammation caused by neurotropic viruses may lead to benign paroxysmal positional vertigo picture. For all these reasons, in benign paroxysmal positional vertigo physiopathology, there must be other factors besides particle debris in semicircular canals.

KEYWORDS: Benign paroxysmal positional vertigo, corticosteroid.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular end-organ disease. It is characterized by a sudden, transient sensation of vertigo. Symptoms are caused by changes in position, such as turning in bed, lying on the bed, lying at the dentist or hairdresser, leaning, or any sudden change in the head's position. Complaints can range from mild to severe dizziness, and nausea and vomiting. Symptoms can last for days, weeks, months, and may recur even after years. Spontaneous remission occurs within days to weeks, and recurrence occurs in approximately 50% of patients.

The rate of BPPV is reported between 17% and 42% in vertiginous patients. It is the most common cause of vertigo in adults. Lifetime prevalence is 3.2% in women, 1.6% in men, and 2.4% overall. Its incidence has been reported as 10.7-64 per 100 000. It can be seen at any age, but it is most common in the fifth and sixth decades of life. The female to male ratio is 2-3: 1, but there is no gender difference in young patients and traumatic cases. It is the most common cause of dizziness after head trauma. It can also be seen during vestibular neuritis and prolonged bed rest. Since delay in diagnosis and treatment of BPPV is common, it impairs patients' quality of life. However, its diagnosis is easy and can be treated in-office.[1]

Dix and Hallpike[2] used the term "benign paroxysmal positional vertigo" for the first time and gave their name to the provocative positional test. The diagnostic criteria published by Barany Society for BPPV included: recurrent positional vertigo or dizziness attacks triggered by lying down or returning to the other side while in the supine position, Dix–Hallpike maneuver or lateral reclining maneuver (Semont's diagnostic maneuver) triggering positional nystagmus after a short latency, nystagmus in the form of a combination of torsional and vertical nystagmus toward the underlying ear, and typically less than 1-minute persistence; these findings could not be linked to any other disease.[3]

Since Adler's first definition in 1897 and Barany in 1921, different inner ear areas have been considered as the source of the disease, such as utricle, saccule, semicircular canals (SCCs), superior vestibular artery, and vestibular nerve. For these, medical and surgical

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treatments with different success rates were applied. Previously, BPPV was thought to be utricular origin. In 1952, Dix and Hallpike[2] thought that the disease was caused by utricle, due to the absence of otolithic membrane, disorganization of the sensory epithelium, specific tissue changes in the connective tissue under the epithelium, and normal-appearing SCCs in histopathological examination. They thought that the recovery of intractable BPPV and related nystagmus in a patient undergoing labyrinthectomy also supports utricular pathology.[2] Cawthorne and Hallpike[4] observed the abnormal utriculus in the autopsy of a patient with recurrent BPPV and supported the utricular pathology. Citron and Hallpike[5] treated BPPV in 1962 with vestibular neurectomy and supported utricular pathology.

When Gacek[6] studied the temporal bone (TB) of 5 patients with BPPV, he found that the significant pathological changes were loss in 50% of ganglion cells and neurons and abnormal saccular ganglion cells in the superior and inferior vestibular areas. He thought that his observations supported the concept that BPPV was caused by the loss of the otolith organs' inhibitory effect on the canal sensory organs. Lindsay and Hemenway,[7] in 1956, detected completely degenerated superior vestibular ganglion, well-preserved otolith organs, and inferior vestibular ganglion in a TB examination of a patient with BPPV, so they thought that BPPV was caused by the occlusion of the superior vestibular artery supplying these structures.

Later, Schuknecht[8,9] pointed to the semicircular canal system. He thought that the relatively more massive debris, consisting of degenerated otoconia separated from the utricular macula, adhered to the posterior SCC cupula (cupulolithiasis). He stated that the most crucial factor in etiology is the spontaneous degeneration of the utricular otolithic membrane.

Since the ampulla of the posterior SCC is in the most inferior position of the labyrinth, sediment from the superior part of the labyrinth was collected here because of the gravity. However, the cupulolithiasis theory did not explain the short duration of nystagmus, the reverse nystagmus when the patient became seated, the end of the attack even after the continuation of the provocative head position, fatigue in repeated tests, and prolonged remission periods in some patients.

Then, freely floating intracanalicular debris was blamed in the canal endolymph (canalolithiasis).[10]

In the following years, various factors such as latent neurotropic viral infections, low serum vitamin D level, bone metabolism diseases, and local ischemia as a result of vasospasm in the labyrinthine arteries associated with migraine were accused.[11-14]

In the last 50 years, cupulolithiasis–canalolithiasis (the mechanical theory) has become the accepted theory, and medical-surgical treatments based on this theory have been successfully applied.

However, we are still unable to clarify the physiopathology of BPPV fully. None of these theories, including mechanical theory, is sufficient to explain all the features of BPPV listed below:

1. latency, limited time, and fatigue of rotatory nystagmus despite constant provocation,
2. long recovery periods between BPPV attacks (sometimes years),
3. the absence of nystagmus despite subjective symptoms with provocation in some patients, and
4. the absence of basophilic deposits in the cupula and membranous posterior canal in the TB histological examination of many patients with a BPPV history.

The mechanical theory is based on very few histological studies; even today, these few studies are referenced. However, these studies' findings are insufficient to hold only the mechanical theory responsible for BPPV's entire clinical appearance. All the patients in these studies are elderly patients. Moreover, all patients with BPPV do not have debris, and the debris is observed in asymptomatic healthy people.

Therefore, basophilic deposits must be an associated morphological finding with aging or degenerated labyrinth, and it is doubtful for the debris to be responsible for BPPV physiopathology alone.

This study aims to review the anatomical, histological, and clinical evidence on BPPV and questions the importance of mechanical theory in the physiopathology of BPPV. For this purpose, a literature review was performed, and studies examining the debridement microscopically or macroscopically in patients with BPPV were separated and reevaluated. It was discussed whether debris is caused by otoliths and whether it is the only reason for positional nystagmus.

An electronic search was performed using the most important scientific databases, such as PubMed, EMBASE, and Cochrane Library, for published histological examinations on BPPV. The articles were identified using a search of the database using the keyword "Benign Paroxysmal Positional Vertigo," and a total number of 2200 trials were included. The search included articles published from 1963 to 2021. The date of the most recent search was December 2020. No language or time limitation was applied. Fourteen articles demonstrating debris microscopically or macroscopically in patients with BPPV have been studied.

In the literature, 14 studies have been identified demonstrating debris either microscopically or macroscopically or studying the TB to exhibit the BPPV physiopathology. Six of them are case report, 5 of them are TB histological study, 1 of them is case report + TB histological study, 2 of them are macroscopic study. The features and comments of the studies are shown in Table 1 and discussed in the "Discussion" section.

Clinical and Research Consequences

In cupulolithiasis, the particles are adhered to the cupula, while in canalolithiasis, the separated particles from the utricular macula enter the SCC from the non-ampullar part, freely float in the canal, and create an endolymph flow during a position change. The observation of particles in the posterior SCC supported these theories. However, in the literature, the number of articles demonstrating the particles in SCCs is extremely low. Even today, in articles published about BPPV, these few articles and the old ones are referenced. When these articles were analyzed, it is noteworthy that there was little evidence to support the mechanical theory. Histological articles in the literature on which mechanical theory is based on are shown in Table 1.

Table 1. Publications Examining the Presence of Debris in the Labyrinth Microscopically or Macroscopically in the Literature

Author	Year	Study Design	Number of Patients	Age of Patient	Findings (Microscopic or Macroscopic)	BPPV Symptomatology	Comment of Authors
Dix–Hallpike	1952	Case report-histologic study	1 case	40	Normal appearing SCCs, severe degeneration in utriculus, sacculus and cochlea, degenerating sensory epithelium of utriculus, stroma thickened and infiltrated with cells, missing in otolithic membrane	Severe BPPV	
Lindsay–Hemenway	1956	Case report-histologic study	1 case	78	Degeneration in part of superior vestibular nerve, ampulla of posterior SCC protected, missing in utricular otolithic membrane	Severe BPPV	Vascular occlusion supplying the anterior vestibular labyrinth
Cawthorne–Hallpike	1957	Case report-histologic study	1 case	59	Severe degeneration in utricular macula, severe degeneration in lateral SCC crista and nerve posterior SCC and crista protected	Severe BPPV	Impaired arterial support due to atheromatous occlusion
Schuknecht	1969	Case report-histologic study	2 cases	68-77	Case 1: basophilic homogenous deposits in the posterior part of posterior SCC cupula Case 2: granular basophilic stained deposits on the membranous wall in the most inferior part of the posterior SCC and attached to the posterior SCC cupula	Paroxysmal positional vertigo	Deposits arise from degenerate inner ear structures
Schuknecht-Ruby	1973	Case report-histologic study Temporal bone histologic study	1 case, 391 temporal bones	87	Case: dense basophilic deposits in the posterior SCC cupula TB: deposits in SCCs in 149 temporal bones (38%)	No vertiginous symptom	Due to postmortem degeneration
Parnes-McClure	1992	Case report-macroscopic examination	2 cases	81-84	Posterior canal occlusion was performed in 21 ears with resistant BPPV, only 2 patients had floating particles in the posterior SCC (the oldest patients in the study)	Resistant BPPV	Particles due to degenerative changes in the inner ear
Moriatry	1992	Temporal bone-histologic study	560 Temporal bones		22% of SCCs have basophilic granular deposits in their cupula, there are microfractures in the otic capsule.	No history of BPPV	Debris is formed because of small hemorrhages due to microfractures.
Kveton	1994	Macroscopic examination	10 cases		9 out of 10 patients operated for acoustic tumor have particles in the membranous labyrinth.	Only 1 patient had preoperative vertigo	Particles may be normal findings.
Naganuma	1996	Temporal bone-histologic study	87 Temporal bones		Basophilic deposit detected in 62% of SCCs, deposits increase with age.	55% of patients have no complaints with the labyrinth.	Otolith presence in SCCs is common but mostly asymptomatic.
Welling	1997	Macroscopic study	99 cases		Translabyrinthine acoustic tumor excision or labyrinthectomy was performed in 73 patients without BPPV, no particles were detected in any of them. Posterior SCC occlusion was performed in 26 patients with BPPV, and particles were detected in only 8.		Degeneration due to age
Bachor	2002	Temporal bone-histologic study	121 cases		186 TB studied, the rate of deposits in SCC cupulae 35/276 (12.7%)		Deposits are result of aging labyrinth

Table 1. Publications Examining the Presence of Debris in the Labyrinth Microscopically or Macroscopically in the Literature (*Contined*)

Author	Year	Study Design	Number of Patients	Age of Patient	Findings (Microscopic or Macroscopic)	BPPV Symptomatology	Comment of Authors
Gacek	2003	Temporal bone-histologic study	5 cases		There is no deposit in 4 TBs, 50% loss of ganglion cells in the superior vestibular part in all, loss of neurons in the inferior vestibular part; 50% in 3 TB and 30% in 2 TB	History of BPPV	BPPV occurs with the loss of inhibitory effect of otolith organs on SCCs.
Kusunoki	2005	Temporal bone-histologic study	23 Temporal bones		All received aminoglycoside treatment within 6 months prior to death, 34.8% basophilic material available in SCCs.	No history of BPPV	Basophilic material due to ototoxicity
Kao	2017	Case report-macroscopic examination	2 cases	59-70	Posterior SCC occlusion was applied, particle detected.	Severe BPPV	Particles are intact and degenerated otoliths separated from the otolithic membrane.

BPPV, benign paroxysmal positional vertigo; SCC, semicircular canal; TB, temporal bone.

Schuknecht[8] published histological findings of the postmortem TBs of 2 cases with paroxysmal positional vertigo in his article in which he used the term "cupulolithiasis" for the first time. In both cases, basophilic stained deposits were detected by adhering to the posterior SCC cupula and in the membranous wall in the most inferior part of the posterior SCC. Utricular and saccular otolithic membranes and the posterior canal cupula of the other ear seemed intact. Since the cupula of the posterior canal of the affected ear and of the other ear were the same, Schuknecht thought that the deposits' source was not the cupula. According to Schuknecht, if the basophilic deposits were produced from the crista-cupular system, the cupula containing the basophilic deposit should have been morphologically different from the cupula that did not contain it. However, since there was no morphological difference between the 2, the source cannot be the crista-cupular system. Schuknecht stated that the sensory epithelium of the utricular and saccular maculae was normal in both ears, the otolithic membranes were intact, the vestibular nerve was normal, and the sensory epithelium of all cristae was intact.

So, where do degenerate otoliths come from?

Schuknecht thought that deposits had calcium carbonate particles from otoconia, but he also reported that other degenerated structures might have caused it. Nevertheless, these patients were 77 and 68 years old when they died and when the histological study was done. As in other articles showing deposits with histological study, the fact that patients are elderly in this study suggests that deposits may result from age-related degeneration. Schuknecht thought that similar deposits detected in 12.3% of the TBs in a study of Ruby might be due to the postmortem degeneration of the utricular otolithic membrane. In the same article, Schuknecht cited 3 studies that published postmortem TB histological studies of patients with paroxysmal positional vertigo. These are studies of Dix and Hallpike in 1952, Lindsay and Hemenway in 1956, and Cawthorne and Hallpike in 1957.

Dix–Hallpike published the TB findings of a 40-year-old woman with severe right sensorineural hearing loss (SNHL) and positional vertigo for 20 years. Attacks appeared when the head took a position with the right ear down. A histological examination found that left labyrinth and right SCCs were normal, but there were severe degenerative changes in utricle, saccule, and cochlea.[2]

Lindsay and Hemenway[7] examined the TBs of a patient who had severe vertigo, vomiting, and dizziness when he turned right at the bed, starting at 65 years old, and continued positional vertigo until his death after 13 years. In the histological study, they observed degeneration only in the area of superior vestibular nerve in the right ear, and they attributed the symptoms of this patient to the occlusion of the vascular supply of the vestibular labyrinth. It is noteworthy that histological examination of this patient was performed at the age of 78.

Cawthorne–Hallpike[4] presented histological findings of a 59-year-old patient who was suffering from a vertigo attack for 2 years on lying on the right side. On examining this patient who had an attack when the positional test was performed making him lie in the supine position with the right ear below, they observed degeneration in the utricular macula and lateral SCC crista. Other inner ear parts were normal. The

authors' comment was that there was an atheromatous occlusion in the artery supplying the right utricle and lateral SCC crista.

In these 3 studies, the utricular macula, cristae of lateral and superior SCC, and superior vestibular nerve degeneration was observed, and the posterior SCC crista and nerve were found to be intact. Schuknecht reported that he had the same opinion as the authors. But while these 3 studies reported degeneration in the utricular macula, Schuknecht reported that utricles and maculae were normal in the 2 TBs he studied. Therefore, with these studies, it is not possible to clearly say that positional vertigo is caused by degeneration of which part of the inner ear.

Schuknecht and Ruby[9] added the third case to the 2 cases in the previous article. In this case, they detected intense basophilic deposits in the posterior SCC cupula, but this patient was 87 years old, meaning that the deposits were probably due to age-related degeneration, and there were no vertiginous symptoms in the history of this patient. In the same article, they studied 391 TBs of 245 people without gross pathology, classified the deposits seen in these TBs as small, medium, and large, and observed 125 small, 20 medium, and 4 large deposits, according to the size of deposits seen in the previous 3 patients (149/245, 38.11%). But there was no information on whether patients with deposits had positional vertigo.

Parnes and McClure[15] showed canalolithiasis in vivo for the first time in 1992. They performed posterior canal occlusion in 21 ears of 20 patients with resistant BPPV and observed free-floating particles in posterior SCC in only 2 patients, but these patients were 81 and 84 years old. They observed that postoperative BPPV symptoms improved in all patients with and without particles in the 3-to-39-month follow-up period. They commented that particles might be due to degenerative changes in the inner ear.

Kao detected free-floating particles in the posterior SCC in 2 patients who had posterior canal occlusion due to BPPV and studied the particles with a scanning electron microscope (SEM).[16] He said they were intact and degenerated otoconia separated from the utricular otolithic membrane to which the particles were attached. However, these patients were aged between 59 and 70 years. He also found that the otoconia obtained from the patient with vestibular neuritis were more degenerated than the patient with primary BPPV. He thought that this might have been due to the difference in the specimen's fixation and preparation process. This suggested that the particles may have formed depending on the age and the preparation and fixation process of the TB specimen.

In all these studies, the deposits observed in the histological examination must have been due to senile degeneration in the labyrinth. Otoconia have been shown to undergo degenerative changes with age.[16] It has been suggested that the particles may also be related to the postmortem TB preparation process. However, while the rate of having deposit in the cupula given by Naganuma[17] in adults was 62.2%, Bachor's[18] rate in the pediatric group between the ages of 10 and the newborn was 12.7%. Bachor thought that if the deposits observed in histological studies were due to postmortem autolysis, the rates given in adult and pediatric age groups should be close because the same fixation methods were used in both groups. Therefore, he thought that the deposits could not be formed due to fixation methods and that the deposits exist in the premortem period.

Particles detected in SCCs are pointed out as the cause of the disease, but there are studies in the literature that exhibit patients who do not have positional vertigo, even though the particle is detected. Moriarty examined 1031 semicircular canals belonging to 566 TBs and detected 22% of the bones with a cupular basophilic deposit. None of these patients had a previous BPPV history. According to Moriarty, if these deposits were really degenerated otoconia originated from utricle or saccule, there would be expected a similar accumulation in maculae of utricle and saccule, but this was not observed in this study. Moreover, the deposits originating from otoconia should have been more on the utricular side of the lateral canal cupula, but there were no statistically significant differences in this series (27% on the utriculopedal side and 22% on the utriculofugal side). So, Moriarty[19] said there should be another explanation for these cupular deposits. He thought that small hemorrhages due to microfractures detected in the otic capsule in the TBs might lead to debris.

Kveton et al[20] performed posterior canal fenestration in 10 patients who underwent acoustic neurinoma excision with a translabyrinthine approach. They detected free-floating particles in membranous canals in 9 patients. When this debris was studied with electron microscope (EM) in 2 patients, these particles were found to have mixed proteineous and mineral content and thought they degenerated otoconia. Although 9 patients had debris in the membranous labyrinth, only 1 of them had preoperative positional vertigo. Naganuma et al[17] examined 87 TBs of 45 people, found basophilic deposits in 1 or more SCC in 55 bones (62.22%), and detected the deposit in all 3 SCCs which was found to be 26% in superior canals, 41% in lateral canals, and 37% in posterior canals.[17] They observed increased rates of deposits with age. According to canalolithiasis or cupulolithiasis theories, the presence of otolith in only 1 canal is sufficient to create BPPV symptoms. However, 55% of these patients had no vertiginous symptoms. Kusunoki[21] found 34.8% basophilic material in the SCC of the TBs of patients who received aminoglycoside therapy within 6 months before death, but there was no history of BPPV in these patients.

These studies support the opinion that the presence of particles in SCCs will not be sufficient to create positional vertigo. There are also studies where the opposite is observed. In other words, in the literature, patients are present with BPPV symptomatology, although they do not show any deposit in histological examination.

Parnes[15] performed posterior canal occlusion in 21 ears with severe BPPV that did not respond to particle repositioning maneuvers (PRM) but observed particles in the posterior canal in only 2 patients. Welling[22] observed particles in posterior SCC in only 8 of 26 patients with BPPV who underwent posterior canal occlusion. Welling[22] thought that the gelatinous layer of the otolithic membrane decreased with age and spontaneous separation of the otoconia from the utricle and saccule would be easier. Gacek[23] reported that basophilic deposits were not detected in the posterior SCC or cupula in TBs of his patients with BPPV. Luryi et al[24] performed posterior semicircular canal occlusion surgery in 26 patients with BPPV and observed 96.2% improvement in the Dix–Hallpike test. However, in the postoperative period, 42.3% BPPV was repeated: 11.5% in the

operated ear and 30.8% in the other ear. Luryi[24] interpreted the high recurrence rate and the emergence of BPPV in the opposite ear due to another pathophysiological factor in patients with BPPV.

The presence of otoconia in SCCs is tried to be explained by 2 theories. First, due to trauma or age-related degeneration, the interconnecting fibrils between the otoconia are weakened, and the otoconia is separated from the otolithic membrane and displaced toward the SCCs (dislodged otoconia). Otoconia can be separated from the gelatinous matrix after age-related changes or demineralization. Second, due to de novo formation of proteinaceous deposits inside the canal. The pathogenesis of age-related otoconial degeneration is not fully understood. Calcium metabolism disorders, such as osteopenia or osteoporosis, may be responsible for decreasing endolymphatic calcium support. Otoconia can be damaged by trauma, medication, inflammation, and, most importantly, age-related decalcification. With advancing age, progressive demineralization causes disruption and disintegration in otoconia.[25-26] Some drugs, such as aminoglycosides, have been shown to disrupt otoconial morphology.[27]

In their study on rats of Jang et al.[28] they observed that degeneration in otoconia increased as the age of the rats increased. They found weakness and fracture in the connection filaments, thickening in the otoconial layer, and a significant increase in the length and width of the otoconia.

Johnsson[29] studied TB in 24 patients over 60 years of age and detected severe to total loss in saccular otoconia and degeneration in utricular otoconia. Ross et al[30] documented the degeneration of human otoconia with age in autopsy specimens with SEM. They observed saccular otoconial degeneration in all patients over 50 years of age and stated that the degree of degeneration increases with increasing age.

In an animal study, Andrade et al[26] observed that the fibrils binding the otoconia together had weakened or disappeared as a result of demineralization with age in mouses. In these parts, fibrils cannot hold on to other otoconia. This leads to otoconia separating from others and releasing in the endolymphatic cavity. Walther et al[31] studied otoconial morphology in 5 patients operated for vestibular schwannoma. They found that otoconial degeneration increased with age: fissures in otoconia, surface roughening, enlargement in pores, disruption in the typical external bulbous pattern, and eventually loss of characteristic appearance. As a result, fragmentation and degeneration occur in the otolithic membrane with age and parts of the otolithic membrane are mobilized with the associated otoconia. Due to gravity, they migrate to the lowest parts of the SCCs and become free-floating debris. Otoliths found in SCCs may be due to advancing age or because of trauma or demineralization.

The absence of positional vertigo in some people with free or bounded particles and the absence of free or bounded particles in some patients with positional vertigo undermine the theory linking all clinical findings to otoliths BPPV. In addition to all these data showing that deposits in SCCs are insufficient to explain the BPPV symptomatology, the anatomical examination also suspects us. According to Anson–Donaldson,[32] the posterior SSC ampulla opens to the inferior part of the utricle. Grays Anatomy[33] also described the macula of the utricle to be located on the roof and medial wall of the vestibule and described that the posterior canal also opens into the lower part of the vestibule. Buckingham[34] obtained the same anatomical results in 130 TBs examined with 2 mm sections. Therefore, the utricular macula is located in the superior part of the vestibule and the ampulla of the posterior SSC opens to the hollow part of the utricle from the inferior. Particle repositioning maneuvers allow free-floating otoliths in the semicircular canal to be repositioned in the utricle by giving different head and neck positions. These maneuvers do not eliminate otoliths, only reposition them in the labyrinth. There are no studies in the literature reporting on how otoliths take position after maneuvers. With the PRM, loose otoliths will pass through the common crus and fall into both the utricular macula and ampulla of the posterior SSC, that is, to the most inferior part.[34]

The anatomical study of Buckingham has shown that maneuvers direct the otoliths toward the utricular macula, but when the patient is in an erect position, some of the otoliths should fall into the utriculopedal part of the posterior SCC. Here, otoliths are expected to continue to make the posterior SSC susceptible to gravity and continue with complaints by provocative head movements, but studies show that most patients recover with PRM.[1,35] Also, according to Anson Donaldson,[36] the lateral SCC is the closest structure to the utricular macula. When the supine patient turns his head, the otoliths should escape and stimulate to the closer lateral SCC, not the posterior SCC. However, the rate of lateral canal BPPV given in the literature is between 15% and 20%. Therefore, the explanation of BPPV emerging due to the debris in SCCs is insufficient in explaining the clinical picture from anatomical aspect. The necessity of lateral canal pathology to be at the forefront has been supported by clinical studies as well as anatomical studies. Baloh[37] detected vestibular paresis in 39% for caloric tests in 240 patients with BPPV, mostly on the diseased side. Katsarkas[38] found the caloric test to be normal in the inactive phase of the disease, while abnormal results were more common in the active phase. Korres[39] applied a caloric test to 122 BPPV patients and observed 27% vestibular paresis, 17% direction superiority, 8% channel paresis, and direction superiority together. Despite the posterior canal involvement being much higher in this disease, why do we observe signs of abnormal lateral canal function?

Kim et al[40] found the modified Gufoni maneuver's treatment efficacy and the head-shaking maneuver remarkably close in the apogeotropic horizontal canal BPPV. Head shaking separates the debris from the cupula, but how does it send the particles into the vestibule? A significant number of patients with BPPV state that the dizziness complaint occurs when they first lie on the bed, or when they return from one side to the other, or when they first get out of bed in the morning. In Kim's series, most patients reported that their complaints started when they turned to one side in bed. What is the relation of BPPV with sleep or sleeping position? Involuntary movements during sleep have been recorded.[41] Accordingly, long inactive periods follow major posture changes. In the first 6 hours of sleep, an average of 12 posture changes was detected. In these, the trunk rotates at least 45 degrees or at least 3 limbs were displaced. Most of these movements are in the lateral canal plan and should provoke the lateral canal vertigo. Therefore, the lateral canal vertigo should be seen as often as the posterior canal vertigo. Also, as Buckingham[35] pointed out, the utricular macula is located close to the ampullae of superior and lateral canals. In 3D sections taken from the utricular macula and superior-lateral canals of TB, loose otoliths appear to be easier to escape to the lateral canal cupula when the patient in the supine

position rotates from one side to the other side. For these reasons, the lateral canal should be more prone to cupulolithiasis or canalolithiasis than the posterior canal.

According to this information, lateral canal type vertigo should be seen more frequently. Nevertheless, this is not the case in the clinical practice. This can be proved by the type of nystagmus in the Dix–Hallpike test, the high success rate of PRMs, and the improvement of symptoms with the section of the posterior ampullar nerve on the same side. However, the less common occurrence of lateral SCC-BPPV may be due to the reason that most patients recover spontaneously and therefore do not consult a doctor. The short duration of the natural course of lateral SCC-BPPV also causes a low number of patients. Shim et al[42] reported the time between the onset and the end of vertigo in patients with lateral SCC-BPPV who were not given any treatment. They found that this period was 6.7 days in patients with geotropic type lateral SCC-BPPV, while it was 3.7 days in patients with apogeotropic type lateral SCC-BPPV. They also consider that the natural course of lateral SCC-BPPV is shorter than those reported in previous studies.

In posterior SCC-BPPV, the Epley maneuver has an early effect that rapidly reduces positional nystagmus. However, the same effect is seen when Dix–Hallpike tests are repeated. Imai et al[43] thought that this early effect was not the therapeutic effect of the Epley maneuver but the fatigability of BPPV. The authors divided patients with posterior SCC-BPPV into 2 groups: they did not give any interval between head positions during the Epley maneuver and gave a 3-minute interval between positions in the second group. Between both groups, they experienced that, in terms of positional nystagmus, setting interval time was unnecessary for the early effect of maneuver. Since this early effect decreased after 30 minutes in the Epley maneuver, which did not apply interval time, they thought that the early effect of reducing positional nystagmus was more related to BPPV fatigue than the therapeutic effect of the maneuver. Therefore, since we have replaced the otoliths to the utriculus with reposition maneuvers, we think that the positional nystagmus is lost, but this study supports that the improvement depends not on the maneuver but on the fatigue of the disease, that is, its natural course.

All these histological, clinical, and anatomical findings suggest that there should be other mechanisms in BPPV physiopathology and the emergence of vertigo and nystagmus.

Bojrab et al[44] attribute the imbalance in patients with BPPV to dysfunction in the tonic resting firing rate of hairy cells in otolithic organs. Damage in the otolithic organs can be caused by factors such as vascular ischemia inflammation trauma, and secondary elevation occurs in the neuroepithelial layer. Depending on whether the elevation turns to complete separation, the BPPV clinic develops or does not develop in patients. In BPPV, the main pathological change may be the degeneration in vestibular ganglia and vestibular neurons but not change in receptor sensitivity (i.e., sensitivity caused by otoliths). The cause of this degeneration may be the inflammation caused by the reactivation of latent neurotropic viral infection or inflammation caused by stress hormones.

Gacek[23] examined the TBs of patients with BPPV and did not find deposits in the posterior SCC or cupula but detected degeneration and perineural inflammatory changes in the vestibular ganglion and vestibular nerve. This degeneration is similar to the sensory ganglion cell degeneration seen in neurotropic virus inflammation.[11,45] Members of the alpha herpes virus group (herpes simplex 1 and 2 and herpes zoster) are the most likely viral agents because they are both found in the sensory ganglia and have a high affinity for sensory ganglia.[12] Viral herpes simplex virus DNA fragments have also been detected in other cranial neuropathies. In the ears with BPPV, frequent occurrence of Meniere, vestibular neuritis, idiopathic facial paralysis, and other cranial neuropathies also clinically support the viral cause in BPPV. The inflammation and degeneration pattern observed in neurotropic viral involvement has also been demonstrated histologically in the TBs of patients with Meniere, vestibular neuritis, BPPV, and idiopathic facial paralysis.[11] Neural degeneration resulting from virus reactivation may impair vestibular function. Citron–Hallpike[5] and Brandt[46] also mentioned that a neural component might be responsible for BPPV and explained the properties that cannot be explained by the mechanical concept. Studies have shown that HSV-1 DNA is found in the vestibular ganglia and in the vestibular nuclei.[47] Arbusow et al[48] studied HSV-1 DNA in 21 randomly selected TBs by polymerase chain reaction technique and observed 48% in labyrinths, 62% in vestibular ganglia, and 57% in geniculate ganglia. According to Arbusow, these findings indicate that inflammation in the vestibular neuritis can also affect the labyrinth, causing unilateral acute vestibular insufficiency, and BPPV may be a sequel of viral labyrinthitis since BPPV is common in patients with vestibular neuritis. Hanci et al[49] found that HSV-1, HSV-2, and herpes zoster viral serology values were higher in patients with BPPV than patients in the control group and thought that viral infections triggered BPPV attacks by causing vestibulopathy. Gacek[50] argues that vestibulopathy is caused by the reactivation of latent neurotropic viruses in the vestibular ganglia. Also, he reported an improvement of 90% in vestibular neuritis and Meniere and 66% in BPPV with 3 weeks of antiviral medication treatment. He thought that observing an excellent clinical response with antiviral therapy is the clinical proof of viral neuropathy. After vestibular neuritis, 10-15% BPPV is seen in the same ear and is more resistant to treatment.[51,52]

It is unclear how vestibular neuritis causes otoconial loss, so there must be a different situation than just neuritis. These clinical observations suggest that a neurotropic virus reacting because of stress later in life may cause a clinical picture. This stress factor can be psychological or physiological stress. To change with the factors such as virus type, virus load, the resistance of the host, and the inflamed part of the vestibule, the emerging clinical picture as well changes, and it appears as BPPV, vestibular neuritis, or other vestibulopathy. The condition leading to vestibulopathy is inflammation, not the virus itself. Inflammation may also explain our ability to have an effective clinical response to steroids, a potent anti-inflammatory agent. Steroid treatment has been successful in BPPV cases resistant to maneuver therapy.[53]

It is our clinical observation that patients with BPPV have more attacks during periods of psychological stress. A neuroanatomic connection has been demonstrated between the vestibular system and the monoaminergic and noradrenergic systems that regulate anxiety and mood.[54] Therefore, the unilateral vestibular deficit in peripheral vestibulopathy may cause susceptibility to psychiatric comorbidity and vice versa. Patients with dizziness often complain of anxiety and

depression, and patients with psychiatric problems also suffer from dizziness or vertigo. Therefore, there should be a connection between the vestibular system and the systems processing the emotional state. Lahmann et al[55] found psychiatric comorbidity in approximately half of the patients with vertigo/dizziness complaints. Psychiatric comorbidity is high in these patients, especially in patients with vestibular migraine. Best[56] thought that specific vestibular syndromes, such as vestibular migraine or Meniere, played a trigger-pulling role for the secondary somatoform disease. Ried[57] thought that vestibular nuclei were hypoactive in patients with depression and may have an asymmetry at the level of the brain stem or neural centers. Similarly, in patients with mood disorders, BPPV incidence was significantly higher compared to the control group.[58] These data suggest that the reason that triggered the attack in BPPV may be psychological.

CONCLUSION

The debris we observe in SCCs is the result of degeneration in the labyrinth. This degeneration increases with age. The observation of debris in TB studies in patients with BPPV symptomatology does not indicate a direct relationship between BPPV and debris. Debris is a part of the already aging labyrinth. Almost all patients are elderly in TB studies with BPPV, so debris should be expected in these patients already.

The absence of positional vertigo in some patients with debris observed within the SCCs clinically or histologically and the absence of debris in some patients with the BPPV symptomatology make the accusation of debris from all clinical findings meaningless. In BPPV, just the presence of debris, whether freely floating or adhered to the cupula, may not be responsible for positional nystagmus.

Otoliths must have a role in BPPV, as there is a complaint of dizziness with a change in position, and we may treat the symptoms with the maneuvers. But in physiopathology of BPPV, SCCs, utricle, and saccule might all get affected together and become a vestibulopathy.

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