

Risk Factors for Recurrent Benign Paroxysmal Positional Vertigo

Subjects: Otorhinolaryngology

Contributor: Ioanna Sfakianaki

Benign paroxysmal positional vertigo (BPPV) is the commonest peripheral vestibular condition encountered in a neurotology clinic and it accounts for about 20% to 30% of all the vestibular complaints. The mechanism of BPPV has been based on dislodged otoliths that leave the utricle and freely float in the semicircular canals or attach to the cupula, making the labyrinth sensitive to gravitational forces. BPPV is characterized by recurrent and brief vertigo with corresponding nystagmus when extending or turning the neck, getting up or lying down, or rolling over in bed.

Keywords: BPPV ; BPPV recurrence ; risk factors

1. BPPV recurrence

The BPPV recurrence has been defined as the reappearance of positional vertigo and nystagmus after at least one month from the execution of an effective CRT (canalith repositioning therapy) ^[1]. The frequent recurrence of BPPV may cause great inconvenience in the daily life of patients with reoccurring BPPV. It is found that BPPV can be associated with other comorbidity diseases, including hypertension, diabetes, thyroid disorders, hyperlipidemia, and osteoporosis and may be responsible for increased frequency of recurrence of BPPV following treatment ^[2]. If such a correlation between common comorbidities and BPPV exists, appropriate treatment of these conditions may be useful in limiting chronicity and reducing the frequency of recurrence.

2. Risk Factors for the Recurrence of BPPV

2.1. Age

Progressive demineralization with advancing age leads to degradation, fragmentation and detachment of utricular otoconia, resulting in BPPV ^[3]. Additionally, the higher number of recurrences in the elderly patients might be explained by the reduction in daily activities, limited mobility, fatigue and increase in falls ^{[4][5][6]}. Whether age represents an independent prognostic factor is controversial. Contrary to studies ^{[7][8]} the recurrence rate was demonstrated to be increased with advancing age ^{[9][4]}. In studies with large samples, it has been shown that patients older than 40 years ^[10], or 50 years ^[5], or 65 years ^[11] or in the sixth ^[11] or mainly seventh decade of age ^[2] were more likely to relapse. Picciotti et al. ^[9] supported that the risk for recurrence of BPPV was found to be 1.6 times more in patients older than 65 years compared to younger than 65 years; they also noted that the presence of comorbidity (hypertension, diabetes, vascular diseases) might increase the rate of recurrence in aged patients.

2.2. Gender

BPPV is frequent in females older than 50 years old ^[12]. This trend could be attributed to the increased prevalence of osteoporosis and osteopenia in postmenopausal women ^{[13][14]}, due to the decrease in estrogen secretion (as discussed below). In contrast to age, fewer studies ^{[15][6]} have supported that females were more likely to exhibit recurrences of BPPV compared to studies in which the recurrence was shown to not significantly relate to gender ^{[4][10]}. However, according to a very recent meta-analysis ^[13], females were more prone to relapse.

2.3. Meniere's Disease

Meniere's disease is commonly associated with BPPV. However, this association is still ambiguous and could be attributed to the repeated distention of the membranous labyrinth due to hydrops, which may lead to otoconia detachment, loss of resilience and partial collapse of the semicircular canal; the resulted partial obstruction prevents the otoliths from returning to vestibule during the repositioning maneuvers, increasing the rate of treatment failure ^[16]. Partial obstruction

may also be due to a dilated saccule or adhesion of otoliths to the membranous labyrinth ^[17]. It has been reported that BPPV patients with Meniere's disease have a 6.009-fold higher risk of recurrence compared to those without Meniere's disease ^[6], or a 35% recurrence rate when endolymphatic hydrops and BPPV were associated ^[18]. However, Luryi et al. ^[19] did not support the association between BPPV recurrence with pre-existing Meniere's disease, reporting that signs and symptoms of Meniere's disease may be conflated with symptoms of concurrent BPPV. Patients with BPPV and Meniere's disease required more canal repositioning maneuvers than those with idiopathic BPPV without Meniere's disease ^[18].

2.4. Trauma

Trauma is considered one of the most common causes of secondary BPPV ^{[20][21]}. The nature and severity of traumas are diverse and include head trauma, whiplash injury, head and neck surgery.

There are certain difficulties in assessing trauma as a risk factor of recurrence. Firstly, there is high heterogeneity in the type and the severity of trauma, as well as on the intervals between the traumatic event and the diagnosis of BPPV due to other possible medical issues that patients experience after the event. In addition, the repositioning maneuvers in patients with severe traumas could cause pain and discomfort; therefore, in some cases, they are avoided. In most studies of our review, the cohort size was small, and the information provided about the nature of trauma was insufficient. Thus, more prospective studies with more precise data about the history and the clinical characteristics of traumatic BPPV are necessary, in order to clarify the role of trauma in BPPV.

2.5. Osteoporosis

Otoconia are a result of inorganic calcium carbonate deposited onto an organic matrix core composed of glycoproteins, mainly otoconin 90 ^{[22][23][24]}. In patients with BPPV and osteoporosis, calcium metabolism failure may be present as a common pathogenesis, leading to the synthesis of atrophic fragile otoliths ^[12].

There has been controversy about the implication of osteoporosis on the recurrence of BPPV. Babac et al. ^[5] found that osteoporosis is a potential risk factor for poor treatment results but not for recurrence. Kim et al. found ^[1] that decreased mineral density (BMD) did not show significant association with BPPV recurrence but showed a significant relation with BPPV occurrence. As a study result similar to Kim et al., Yang et al. ^[23] found BMD in women is associated with the occurrence of BPPV, though a low BMD and age correlate with the recurrence of BPPV. De Stefano et al. ^[25], in a multicenter observational study, found that osteoporosis was related to an increased risk of relapse when it was in combination with other comorbidities and defined "groups of risk". Contrary to the above, a few studies have demonstrated an apparent association between BPPV recurrence and BMD score. Yamanaka et al. ^[12] did not find a clinical association between BPPV and osteoporosis but the results of his study suggest that osteoporosis is a risk factor for BPPV recurrence and that the prognosis of the BPPV might be clinically predicted by BMD reduction. Talaat et al. ^[22] in their study found that there was an association between reduced BMD and development/recurrence of BPPV. In a retrospective chart review, Mikulec et al. ^[26] found a significant negative association between BPPV and treated osteoporosis in women aged 51 to 60 years suggesting the possibility that anti-osteoporotic medication may provide protection against BPPV.

These controversies may be explained by different methodologies to measure osteoporotic changes (location for measuring BMD, bone turnover markers), different definitions of BPPV recurrence and follow-up and various distributions of age or gender in study populations. In particular, most of the studies included women, especially older women because BPPV is more common in women between 41 to 61 years old. In addition, most of the studies are retrospective studies where it is difficult to elucidate causal relationships between the recurrence of BPPV and variables including BMD.

2.6. Vitamin D

Vitamin D plays a crucial role in the homeostasis of calcium and phosphorus. Normal serum level of vitamin D is essential for the development of normal otoconia through keeping the calcium concentration in the vestibular endolymph at a normal critical level ^{[27][28]}. The epithelial Ca^{2+} channel transport system, $\text{Na}^+/\text{Ca}^{2+}$ exchangers, and plasma membrane Ca^{2+} pumps expressed in the inner ear contribute to this critical balance of calcium levels by transepithelial absorption of Ca^{2+} from the endolymph of the inner ear ^[29]. Vitamin D receptors in the epithelial cells of the inner ear regulate the expression of some Ca^{2+} binding proteins ^{[30][22][23]}. Therefore, it has been suggested that vitamin D deficiency also contributes to the development and recurrence of BPPV by abnormal calcium metabolism in the inner ear ^[23]. Rhim et al. ^[30] found that vitamin D affects BPPV as a recurrence factor independent of age, gender, follow-up period and type of BPPV. Talaat et al. ^[22] found that low levels of Vitamin D were related to the development of BPPV while very low levels were associated with recurrence of BPPV. Hence, in the following study, Talaat et al. ^[31] analyzed the effect of treatment

of severe vitamin D deficiency on the recurrence rate of BPPV and found that improvement of serum 25-hydroxyvitamin D3 levels is associated with a substantial decrease in recurrence of BPPV. On the contrary, Yang et al. [23] found that the levels of vitamin D are significantly decreased in men with idiopathic BPPV but they are not associated with the recurrence of BPPV. Similarly, Sreenivas et al. [2] found that the recurrence among patients with vitamin D deficiency was not statistically significant. They assumed that there are significant differences between bone and otoconia formation and this could be partially explained by the fact that the calcium for otoconia formation comes from the endolymph; therefore they speculated that serum markers of turnover are not directly involved in the pathogenesis of BPPV [2].

In most of the studies, blood samples were not obtained at a constant time. Given that there is seasonality of vitamin D, it is critical that future studies should take more parameters into account that affect vitamin D levels such as season, country's climate, lifestyle and skin color.

2.7. Diabetes Mellitus/Hyperinsulinism/Hyperglycemia

Changes in glucose metabolism have been associated with a high prevalence of inner ear disorders, hence with BPPV occurrence and recurrence [32][33][34]. These metabolic disorders can act as a principal etiologic factor in vestibular dysfunction, as well as an aggravating factor of a pre-existing vestibular disorder [35]. Yoda et al. [34] reviewed temporal bones of patients with type 1 diabetes and found that they exhibit a much higher prevalence of migration of otocone debris coming from the utricle, compared to healthy patients. In addition, they found that this difference was associated with the duration of the disease. D' Silva et al. [36] reported a higher prevalence of BPPV in patients with type 2 diabetes and found that this association was mediated by hypertension. The pathophysiologic mechanism for this correlation is still elusive. Hyperglycemia increases vascular resistance by inhibiting nitric oxide-related vasodilation, thus a combination of hypertension and diabetes may lead to tissue hypoxia and cochleovestibular degeneration [36]. In diabetes the histopathological changes of microangiopathy and vestibular neuropathy are present. Therefore, diabetes-associated neuropathy and vasculopathy as well as microvascular damage, including atherosclerosis, contribute to otoconial degeneration and thus precipitate BPPV [2][37]. In addition, diabetic patients have a poorer capacity for recovery from mild insults, such as viral infections or mild trauma, making these insults more severe [2]. Furthermore, these patients present mutations in the BETA2/NeuroD1 gene which is essential for the normal development of the sensory epithelia of the cochlea, utricle, saccule, and crista ampullaris [38]. On the other hand, hyperinsulinism may disrupt inner ear homeostasis and alter the ionic and metabolic characteristics of the stria vascularis, which is responsible for maintaining endocochlear potential through potassium secretion in the endolymphatic space [33][35]. The inner ear is also affected by hyperinsulinism due to a large number of the insulin receptors present in the endolymphatic sac [32].

In our review, Webster et al. [32] in a prospective study, found that both hyperinsulinism and hyperglycemia behaved as a risk factor for recurrence of idiopathic BPPV and also that a normal glucose tolerance test acted as a protective factor. De Stefano et al. [25] and Messina et al. [37] conducted multicenter observational studies with a large number of subjects. They evaluated the correlation between comorbidities and recurrent episodes of BPPV and found, among other things, that the presence of diabetes is associated with a statistically significant increased risk of recurrence. Picciotti et al. [9] also found that diabetes was associated with the recurrence of BPPV and that in the recurrent group, patients with more than one comorbidity were significantly more numerous compared with patients with one comorbidity. In line with the abovementioned studies, Kim et al. [1] in a smaller study group, found that comorbidities of diabetes and hypertension were associated with recurrence of BPPV. On the other hand, Sreenivas et al. [2] found a significant association between recurrence of BPPV and diabetes mellitus but not hypertension. However, there are few recent studies that found no significant rate of recurrence among diabetic patients. Specifically, Luryi et al. [19] and Zhu et al. [6] in two large single-institution studies of recurrence of BPPV, found no association between recurrence and diabetes mellitus. Wei et al. [39] in a smaller retrospective study, also did not find a correlation between the presence of comorbidities in general and diabetes mellitus in particular and increased recurrence rates of BPPV.

It seems that diabetes mellitus, as with other comorbidities, plays an important role in BPPV occurrence and recurrence. However, most studies were observational studies that did not investigate whether the patients had a good glucose control (hemoglobin A1C levels), or provide information about subcategories of diabetes (Type 1 versus Type 2), resulting in a limitation of potential therapeutic guidance. Therefore, further studies should be conducted in order to evaluate the possibility that proper treatment may reduce the prevalence and recurrence of BPPV.

2.8. Vascular Comorbidities (Hypertension, Hyperlipidemia, Cardiovascular Disease)

Numerous epidemiological studies have shown a possible association between BPPV and cardiovascular risk factors [25][9][1][37][40]. These studies support the hypothesis of a vascular role in the aetiopathogenesis of BPPV and its recurrence. Specifically, otoconial detachment from the otolith membrane might be facilitated by microvascular modification and

ischemia, further enhanced by hypertensive peaks [9][41]. Furthermore, the blood supply to the inner ear is a terminal circulation, thus any occlusion of the AICA (anterior inferior cerebellar artery) or VBA (vertebrobasilar artery) can cause an ischemic event, leading to audio-vestibular disorders [25][37]. The vestibular system is degraded with age and as a result of changes caused by hypertension and atherosclerosis, resulting in progressive detachment of otoconia from the otolithic membrane [40]. Therefore, multiple systemic diseases increase the recurrence rate [25][9][37].

In this review, most of the studies found that patients with BPPV comorbid with hypertension had an increased recurrence rate of BPPV [25][9][1][6][37][40].

The role of vascular comorbidities in the recurrence of BPPV is still questionable. There are certain difficulties in quantifying clinical data, especially in observational studies, due to the diversity of comorbidities and the plurality of treatments. Moreover, the follow-up period in most of the studies does not provide the time to detect all events of recurrence. In addition, a lot of patients fail to attend follow-up visits or experience a transient recurrence with a rapid resolution of symptoms. However, it seems that hyperlipidemia and hypertension have a significant association with the recurrence of BPPV. Therefore, appropriate treatment of these conditions may be useful in limiting the frequency of recurrence.

2.9. Migraine

Migraine has long been associated with vertigo, with studies suggesting that patients suffering from migraine are two to three times more likely to suffer from vertigo, compared to the headache-free controls [42][43][44]. Moreover, migraine was found to be three times more common in patients with BPPV of an unknown cause than in those with BPPV secondary to trauma or surgical procedures [45]. The mechanisms by which this association arises are not well understood. One of the proposed theories suggests that migraine causes vasospasm of the labyrinthine arteries and the subsequent ischemic damage leads to the release of otoconia from the utricle [45]. Recurrent vasospasm is also associated with the oxidative stress of endothelial cells, which is a possible pathogenetic mechanism common to both migraine and BPPV [46][47]. Therefore, it is speculated that patients with migraines have a recurrent vascular damage in the inner ear that disposes to recurrent BPPV [45][42]. In addition, trigeminal nerve stimulation, an underlying pathophysiologic mechanism of migraine, induces fluid extravasation in the cochlea leading to the detachment of otoconia from the otolith organs [48]. Lastly, it has been reported that certain mutations in a Ca^{2+} channel gene, detected in familial hemiplegic migraine, affect the ion channels of the brain as well as those found in the inner ear, causing imbalance of the resting potentials [45][49].

There are few articles in the literature that address the epidemiological relationship between migraine and the occurrence and recurrence of BPPV, despite the fact that there is a well-recognized association with vertigo. Ishiyama et al. [45] found increased recurrence rates (77%) in the BPPV with migraine group compared to 66% in the group of BPPV without migraine. Zhu et al. [6] in a large study analysis, also reported that BPPV recurrence was associated with migraine ($p = 0.005$). However, Hilton et al. [50], in a large BPPV cohort, compared the recurrence rates between the BPPV with migraine group and the BPPV without migraine group and found no significant difference (38.3% versus 32.1%). In relatively smaller studies, Babac et al. [5] Kansu et al. [7] and Brandt et al. [11] did not find a significantly higher recurrence of BPPV in patients with BPPV and migraine. It is worthwhile to mention the age distribution of patients with BPPV and migraine. In particular, Ishiyama et al. [45] showed that the age of onset in patients with BPPV without migraine was recorded mostly in older age groups, with a peak in the eighth decade. On the contrary, nearly half (47%) of the patients with onset of BPPV before the age of 50 years old had migraines. Similarly, Hilton et al. [50] found that patients over 60 years old had a lower likelihood of having concurrent BPPV and migraine, whereas younger age was independently associated with concurrent comorbidity of BPPV and migraine.

There is a complex relationship between BPPV and migraine due to the high prevalence of vertigo in migraine patients. Vestibular migraine has been recognized as one of the most common causes of recurrent vertigo occurring in migraine patients [51]. In several cases, vestibular migraine may be episodic and appears to be a BPPV reoccurrence, especially when the patients present with central positional nystagmus. Positional nystagmus is of central type and not due to BPPV when a) it has no latency and beats in a direction not aligned for the plane of a particular semicircular canal (e.g., no difference in the nystagmus vector with right versus left Dix-Hallpike), and b) there was no crescendo-decrescendo pattern to the nystagmus and lack of fatigability [51][52]. Distinguishing between the migraines and BPPV is crucial, because multiple maneuvers for misdiagnosed BPPV in a patient with migraines are uncomfortable, distressing and unnecessary if nystagmus is resulting from a migraine. In this case, the treatment should be targeted in the management of migraine episodes [51].

2.10. Bilateral/Multicanal BPPV

Bilateral and multiple-canal BPPV are less frequent forms of BPPV that typically require a larger number of maneuvers. Korres et al. [4] found increased recurrence rates in BPPV patients with bilateral canal involvement. Perez et al. [53] defined complex BPPV in cases of either BPPV affecting more than one canal or requiring a large number of maneuvers and found that these patients were at higher risk of recurrence. Moreover, they suggested that the labyrinths of patients with complex BPPV underwent inflammatory changes leading to recurrent episodes of BPPV [53]. Babac et al. [5], in a small group of patients with bilateral and multicanal BPPV, did not detect a negative impact of these factors on BPPV recurrence. Similarly, according to other studies [7][30], a significant correlation between bilateral/multicanal involvement of BPPV and BPPV recurrence was not found. Noticeably, the small number of patients suffering from bilateral/multicanal BPPV is a limitation of reaching reliable conclusions on the impact of these variables on BPPV recurrence, thus further investigation is required.

2.11. Cervical Osteoarthritis (Spondylosis)

Cervical spondylosis, also defined as osteoarthritis of the cervical spine, is a common age-related condition. More than 85% of people over the age of 60 are affected by cervical spondylosis [54]. It arises as a result of age-related dehydration of the nucleus pulposus and its collapse, causing bulging of the annulus fibrosus. As the disks dehydrate and shrink, signs of osteoarthritis develop, including bony projections along the edges of bones called osteophytes. These osteophytes cause cord space narrowing [54][55]. There is a deficit of studies examining the effects of cervical spondylosis on BPPV. De Stefano et al. [25] evaluated the relationship between recurrent episodes of BPPV and the most common comorbidities in the elderly population and found that the risk of relapsing BPPV in patients with cervical osteoarthritis increases 3 times; this association became statistically significant when related to the number of recurrences. On the contrary, Wei et al. [39] in a smaller study group with a relatively shorter follow-up period of 6 months, did not detect a correlation between cervical osteoarthritis and increased recurrence rates of BPPV. Li et al. [13] in a systematic review of the risk factor-associated recurrence of BPPV, found that cervical spondylosis, among other systemic diseases, could increase the recurrence of BPPV ($p < 0.05$).

It is possible that cervical spondylosis may favor the recurrence of BPPV. This could be explained by the fact that canalith repositioning procedure (CRP) on patients with dysfunction of the cervical spine is very difficult to be performed, thus leading to improper treatment or early recurrence of BPPV. Martelucci et al. [56] investigated the impact of reduced cervical mobility on CRP efficacy and suggested three pathophysiological mechanisms: (1) Debris could remain in the canal lumen and then return to the ampullary arm, causing the failure of the maneuver. (2) Part of debris could leave the canal while the rest could sprinkle in the endolymph and then accumulate again. Therefore, a transient regression of symptoms followed by an early relapse can occur. (3) The otoconial could relocate into the superior or horizontal semicircular canals, leading to a canal switch.

2.12. Sleep Disorders

Sleep disorders, especially insomnia, are associated with numerous physical and psychiatric health problems [57]. The pathophysiological link between BPPV and sleep disorders is still unclear. It is suggested that bad sleep leads the patients to multiple head movements during the night, therefore dispose them to a higher risk of BPPV relapse [15]. Other potential mechanisms include neuroendocrine dysfunction, caused by increased cortisol levels, as well as activation of inflammation of the nervous system, including vestibular neurons [58]. In addition, about 40% of individuals with insomnia have a comorbid psychiatric condition like anxiety and depression [58], which is known that may serve as the primary cause of vestibular symptoms as well as a risk factor for BPPV recurrence [59][60].

References

1. Kim, S.Y.; Han, S.H.; Kim, Y.H.; Park, M.H. Clinical Features of Recurrence and Osteoporotic Changes in Benign Paroxysmal Positional Vertigo. *Auris Nasus Larynx* 2017, 44, 156–161.
2. Sreenivas, V.; Sima, N.H.; Philip, S. The Role of Comorbidities in Benign Paroxysmal Positional Vertigo. *Ear Nose Throat J.* 2021, 100, NP225–NP230.
3. Agrawal, Y.; Carey, J.P.; Della Santina, C.C.; Schubert, M.C.; Minor, L.B. Disorders of Balance and Vestibular Function in US Adults: Data from the National Health and Nutrition Examination Survey, 2001–2004. *Arch. Intern. Med.* 2009, 169, 938–944.

4. Korres, S.; Balatsouras, D.G.; Ferekidis, E. Prognosis of Patients with Benign Paroxysmal Positional Vertigo Treated with Repositioning Manoeuvres. *J. Laryngol. Otol.* 2006, 120, 528–533.
5. Babac, S.; Djerić, D.; Petrović-Lazić, M.; Arsović, N.; Mikić, A. Why Do Treatment Failure and Recurrences of Benign Paroxysmal Positional Vertigo Occur? *Otol. Neurotol.* 2014, 35, 1105–1110.
6. Zhu, C.T.; Zhao, X.Q.; Ju, Y.; Wang, Y.; Chen, M.M.; Cui, Y. Clinical Characteristics and Risk Factors for the Recurrence of Benign Paroxysmal Positional Vertigo. *Front. Neurol.* 2019, 10, 1190.
7. Kansu, L.; Avci, S.; Yilmaz, I.; Ozluoglu, L.N. Long-Term Follow-up of Patients with Posterior Canal Benign Paroxysmal Positional Vertigo. *Acta Otolaryngol.* 2010, 130, 1009–1012.
8. Faralli, M.; Ricci, G.; Molini, E.; Bressi, T.; Simoncelli, C.; Frenguelli, A.; Division, C.S. Paroxysmal Positional Vertigo: The Role of Age. *Acta Otorhinolaryngol. Ital.* 2006, 26, 25–31.
9. Picciotti, P.M.; Lucidi, D.; De Corso, E.; Meucci, D.; Sergi, B.; Paludetti, G. Comorbidities and Recurrence of Benign Paroxysmal Positional Vertigo: Personal Experience. *Int. J. Audiol.* 2016, 55, 279–284.
10. Rashad, U.M. Long-Term Follow up after Epley's Manoeuvre in Patients with Benign Paroxysmal Positional Vertigo. *J. Laryngol. Otol.* 2009, 123, 69–74.
11. Brandt, T.; Huppert, D.; Hecht, J.; Karch, C.; Strupp, M. Benign Paroxysmal Positioning Vertigo: A Long-Term Follow-up (6–17 Years) of 125 Patients. *Acta Otolaryngol.* 2006, 126, 160–163.
12. Yamanaka, T.; Shirota, S.; Sawai, Y.; Murai, T.; Fujita, N.; Hosoi, H. Osteoporosis as a Risk Factor for the Recurrence of Benign Paroxysmal Positional Vertigo. *Laryngoscope* 2013, 123, 2813–2816.
13. Li, S.; Wang, Z.; Liu, Y.; Cao, J.; Zheng, H.; Jing, Y.; Han, L.; Ma, X.; Xia, R.; Yu, L. Risk Factors for the Recurrence of Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-Analysis. *Ear Nose Throat J.* 2020, 0145561320943362.
14. Vibert, D.; Kompis, M.; Häusler, R. Benign Paroxysmal Positional Vertigo in Older Women May Be Related to Osteoporosis and Osteopenia. *Ann. Otol. Rhinol. Laryngol.* 2003, 112, 885–889.
15. Su, P.; Liu, Y.C.; Lin, H.C. Risk Factors for the Recurrence of Post-Semicircular Canal Benign Paroxysmal Positional Vertigo after Canalith Repositioning. *J. Neurol.* 2016, 263, 45–51.
16. Kutlubayev, M.A.; Xu, Y.; Hornibrook, J. Benign Paroxysmal Positional Vertigo in Meniere's Disease: Systematic Review and Meta-Analysis of Frequency and Clinical Characteristics. *J. Neurol.* 2021, 268, 1608–1614.
17. Balatsouras, D.G.; Ganelis, P.; Aspris, A.; Economou, N.C.; Moukos, A.; Koukoutsis, G. Benign Paroxysmal Positional Vertigo Associated with Meniere's Disease: Epidemiological, Pathophysiologic, Clinical, and Therapeutic Aspects. *Ann. Otol. Rhinol. Laryngol.* 2012, 121, 682–688.
18. Del Rio, M.; Arriaga, M.A. Benign Positional Vertigo: Prognostic Factors. *Otolaryngol.—Head Neck Surg.* 2004, 130, 426–429.
19. Luryi, A.L.; Lawrence, J.; Bojrab, D.I.; LaRouere, M.; Babu, S.; Zappia, J.; Sargent, E.W.; Chan, E.; Naumann, I.; Hong, R.S.; et al. Recurrence in Benign Paroxysmal Positional Vertigo: A Large, Single-Institution Study. *Otol. Neurotol.* 2018, 39, 622–627.
20. Gordon, C.R.; Levite, R.; Joffe, V.; Gadoth, N. Is Posttraumatic Benign Paroxysmal Positional Vertigo Different from the Idiopathic Form? *Arch. Neurol.* 2004, 61, 1590–1593.
21. Chen, J.; Zhang, S.; Cui, K.; Liu, C. Risk Factors for Benign Paroxysmal Positional Vertigo Recurrence: A Systematic Review and Meta-Analysis. *J. Neurol.* 2020, 1–11.
22. Talaat, H.S.; Abuhadied, G.; Talaat, A.S.; Abdelaal, M.S.S. Low Bone Mineral Density and Vitamin D Deficiency in Patients with Benign Positional Paroxysmal Vertigo. *Eur. Arch. Oto-Rhino-Laryngol.* 2015, 272, 2249–2253.
23. Yang, C.J.; Kim, Y.; Lee, H.S.; Park, H.J. Bone Mineral Density and Serum 25-Hydroxyvitamin D in Patients with Idiopathic Benign Paroxysmal Positional Vertigo. *J. Vestib. Res. Equilib. Orientat.* 2018, 27, 287–294.
24. Lundberg, Y.W.; Zhao, X.; Yamoah, E.N. Assembly of the Otoconia Complex to the Macular Sensory Epithelium of the Vestibule. *Brain Res.* 2006, 1091, 47–57.
25. De Stefano, A.; Dispenza, F.; Suarez, H.; Perez-Fernandez, N.; Manrique-Huarte, R.; Ban, J.H.; Kim, M.B.; Strupp, M.; Feil, K.; Oliveira, C.A.; et al. A Multicenter Observational Study on the Role of Comorbidities in the Recurrent Episodes of Benign Paroxysmal Positional Vertigo. *Auris Nasus Larynx* 2014, 41, 31–36.
26. Mikulec, A.A.; Kowalczyk, K.A.; Pfitzinger, M.E.; Harris, D.A.; Jackson, L.E. Negative Association between Treated Osteoporosis and Benign Paroxysmal Positional Vertigo in Women. *J. Laryngol. Otol.* 2010, 124, 374–376.

27. Parham, K.; Leonard, G.; Feinn, R.S.; Lafreniere, D.; Kenny, A.M. Prospective Clinical Investigation of the Relationship between Idiopathic Benign Paroxysmal Positional Vertigo and Bone Turnover: A Pilot Study. *Laryngoscope* 2013, 123, 2834–2839.
28. Jeong, S.H.; Kim, J.S.; Shin, J.W.; Kim, S.; Lee, H.; Lee, A.Y.; Kim, J.M.; Jo, H.; Song, J.; Ghim, Y. Decreased Serum Vitamin D in Idiopathic Benign Paroxysmal Positional Vertigo. *J. Neurol.* 2013, 260, 832–838.
29. Yamauchi, D.; Raveendran, N.N.; Pondugula, S.R.; Kampalli, S.B.; Sanneman, J.D.; Harbidge, D.G.; Marcus, D.C. Vitamin D Upregulates Expression of ECAC1 mRNA in Semicircular Canal. *Biochem. Biophys. Res. Commun.* 2005, 331, 1353–1357.
30. Rhim, G. II Serum Vitamin D and Recurrent Benign Paroxysmal Positional Vertigo. *Laryngoscope Investig. Otolaryngol.* 2016, 1, 150–153.
31. Talaat, H.S.; Kabel, A.M.H.; Khaliel, L.H.; Abuhadied, G.; El-Naga, H.A.E.R.A.; Talaat, A.S. Reduction of Recurrence Rate of Benign Paroxysmal Positional Vertigo by Treatment of Severe Vitamin D Deficiency. *Auris Nasus Larynx* 2016, 43, 237–241.
32. Webster, G.; Sens, P.M.; Salmito, M.C.; Cavalcante, J.D.R.; dos Santos, P.R.B.; da Silva, A.L.M.; de Souza, É.C.F. Hyperinsulinemia and Hyperglycemia: Risk Factors for Recurrence of Benign Paroxysmal Positional Vertigo. *Braz. J. Otorhinolaryngol.* 2015, 81, 347–351.
33. Angeli, R.D.; Lavinsky, L.; Dolganov, A. Alterations in Cochlear Function during Induced Acute Hyperinsulinemia in an Animal Model. *Braz. J. Otorhinolaryngol.* 2009, 75, 760–764.
34. Yoda, S.; Cureoglu, S.; Yildirim-Baylan, M.; Morita, N.; Fukushima, H.; Harada, T.; Paparella, M.M. Association between Type 1 Diabetes Mellitus and Deposits in the Semicircular Canals. *Otolaryngol.—Head Neck Surg.* 2011, 145, 458–462.
35. Paula Serra, A.; de Carvalho Lopes, K.; Doriguetto, R.S.; Freitas Ganança, F. Blood Glucose and Insulin Levels in Patients with Peripheral Vestibular Disease. *Braz. J. Otorhinolaryngol.* 2009, 75, 701–705.
36. D'Silva, L.J.; Staecker, H.; Lin, J.; Sykes, K.J.; Phadnis, M.A.; McMahon, T.M.; Connolly, D.; Sabus, C.H.; Whitney, S. L.; Kludinga, P.M. Retrospective Data Suggests That the Higher Prevalence of Benign Paroxysmal Positional Vertigo in Individuals with Type 2 Diabetes Is Mediated by Hypertension. *J. Vestib. Res. Equilib. Orientat.* 2016, 25, 233–239.
37. Messina, A.; Casani, A.P.; Manfrin, M.; Guidetti, G. Survey Italiana Sulla Vertigine Parossistica Posizionale. *Acta Otorhinolaryngol. Ital.* 2017, 37, 328–335.
38. Liu, M.; Pereira, F.A.; Price, S.D.; Chu, M.J.; Shope, C.; Himes, D.; Eatock, R.A.; Brownell, W.E.; Lysakowski, A.; Tsai, M.J. Essential Role of BETA2/NeuroD1 in Development of the Vestibular and Auditory Systems. *Genes Dev.* 2000, 14, 2839–2854.
39. Wei, W.; Sayyid, Z.N.; Ma, X.; Wang, T.; Dong, Y. Presence of Anxiety and Depression Symptoms Affects the First Time Treatment Efficacy and Recurrence of Benign Paroxysmal Positional Vertigo. *Front. Neurol.* 2018, 9, 178.
40. Tan, J.; Deng, Y.; Zhang, T.; Wang, M. Clinical Characteristics and Treatment Outcomes for Benign Paroxysmal Positional Vertigo Comorbid with Hypertension. *Acta Otolaryngol.* 2017, 137, 482–484.
41. Von Brevern, M.; Radtke, A.; Lezius, F.; Feldmann, M.; Ziese, T.; Lempert, T.; Neuhauser, H. Epidemiology of Benign Paroxysmal Positional Vertigo: A Population Based Study. *J. Neurol. Neurosurg. Psychiatry* 2007, 78, 710–715.
42. Bruss, D.; Abouzari, M.; Sarna, B.; Goshtasbi, K.; Lee, A.; Birkenbeuel, J.; Djalilian, H.R. Migraine Features in Patients With Recurrent Benign Paroxysmal Positional Vertigo. *Otol. Neurotol.* 2021, 42, 461–465.
43. Vuković, V.; Plavec, D.; Galinović, I.; Lovrenčić-Huzjan, A.; Budišić, M.; Demarin, V. Prevalence of Vertigo, Dizziness, and Migrainous Vertigo in Patients with Migraine. *Headache* 2007, 47, 1427–1435.
44. Kuritzky, A.; Ziegler, D.K.; Hassanein, R. Vertigo, Motion Sickness and Migraine. *Headache J. Head Face Pain* 1981, 21, 227–231.
45. Ishiyama, A.; Jacobson, K.M.; Baloh, R.W. Migraine and Benign Positional Vertigo. *Ann. Otol. Rhinol. Laryngol.* 2000, 109, 377–380.
46. Güçlütürk, M.T.; Ünal, Z.N.; Ismi, O.; Çimen, M.B.Y.; Ünal, M. The Role of Oxidative Stress and Inflammatory Mediators in Benign Paroxysmal Positional Vertigo. *J. Int. Adv. Otol.* 2016, 12, 101–105.
47. Neri, M.; Frustaci, A.; Milic, M.; Valdiglesias, V.; Fini, M.; Bonassi, S.; Barbanti, P. A Meta-Analysis of Biomarkers Related to Oxidative Stress and Nitric Oxide Pathway in Migraine. *Cephalalgia* 2015, 35, 931–937.
48. Vass, Z.; Steyger, P.S.; Hordichok, A.J.; Trune, D.R.; Jancsó, G.; Nuttall, A.L. Capsaicin Stimulation of the Cochlea and Electric Stimulation of the Trigeminal Ganglion Mediate Vascular Permeability in Cochlear and Vertebro-Basilar Arteries: A Potential Cause of Inner Ear Dysfunction in Headache. *Neuroscience* 2001, 103, 189–201.

49. Ophoff, R.A.; Terwindt, G.M.; Vergouwe, M.N.; Van Eijk, R.; Oefner, P.J.; Hoffman, S.M.G.; Lamerdin, J.E.; Mohnenweiser, H.W.; Bulman, D.E.; Ferrari, M.; et al. Familial Hemiplegic Migraine and Episodic Ataxia Type-2 Are Caused by Mutations in the Ca²⁺ Channel Gene CACNL1A4. *Cell* 1996, 87, 543–552.
50. Hilton, D.B.; Luryi, A.L.; Bojrab, D.I.; Babu, S.C.; Hong, R.S.; Santiago Rivera, O.J.; Schutt, C.A. Comparison of Associated Comorbid Conditions in Patients with Benign Paroxysmal Positional Vertigo with or without Migraine History: A Large Single Institution Study. *Am. J. Otolaryngol.—Head Neck Med. Surg.* 2020, 41, 102650.
51. Lempert, T.; von Brevern, M. Vestibular Migraine. *Neurol. Clin.* 2019, 37, 695–706.
52. Argat, E.C.; Bradshaw, A.P.; Welgampola, M.S. Benign Positional Vertigo, Its Diagnosis, Treatment and Mimics. *Clin. Neurophysiol. Pract.* 2019, 4, 97–111.
53. Pérez, P.; Franco, V.; Cuesta, P.; Aldama, P.; Alvarez, M.J.; Méndez, J.C. Recurrence of Benign Paroxysmal Positional Vertigo. *Otol. Neurotol.* 2012, 33, 437–443.
54. Kelly, J.C.; Groarke, P.J.; Butler, J.S.; Poynton, A.R.; O'Byrne, J.M. The Natural History and Clinical Syndromes of Degenerative Cervical Spondylosis. *Adv. Orthop.* 2012, 2012, 393642.
55. Bayrak, I.K.; Durmus, D.; Bayrak, A.O.; Dren, B.; Canturk, F. Effect of Cervical Spondylosis on Vertebral Arterial Flow and Its Association with Vertigo. *Clin. Rheumatol.* 2009, 28, 59–64.
56. Martellucci, S.; Attanasio, G.; Ralli, M.; Marcelli, V.; de Vincentiis, M.; Greco, A.; Gallo, A. Does Cervical Range of Motion Affect the Outcomes of Canalith Repositioning Procedures for Posterior Canal Benign Positional Paroxysmal Vertigo? *Am. J. Otolaryngol.—Head Neck Med. Surg.* 2019, 40, 494–498.
57. Fernandez-Mendoza, J.; Vgontzas, A.N. Insomnia and Its Impact on Physical and Mental Health. *Curr. Psychiatry Rep.* 2013, 15, 418.
58. Shih, C.P.; Wang, C.H.; Chung, C.H.; Lin, H.C.; Chen, H.C.; Lee, J.C.; Chien, W.C. Increased Risk of Benign Paroxysmal Positional Vertigo in Patients with Non-Apnea Sleep Disorders: A Nationwide, Population-Based Cohort Study. *J. Clin. Sleep Med.* 2018, 14, 2021–2029.
59. Bronstein, A. (Ed.) *Oxford Textbook of Vertigo and Imbalance*; Oxford University Press: London, UK, 2013; ISBN 9780199608997.
60. Eckhardt-Henn, A.; Dieterich, M. Psychiatric Disorders in Otoneurology Patients. *Neurol. Clin.* 2005, 23, 731–749.

Retrieved from <https://encyclopedia.pub/entry/history/show/44958>