

# Review of the pathology underlying benign paroxysmal positional vertigo

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## Abstract

The pathophysiological mechanism underlying benign paroxysmal positional vertigo (BPPV) is related to free-floating debris/otoliths in the semicircular canal (canalolithiasis) or debris/otoliths attached to the cupula (cupulolithiasis). These debris/otoliths are considered to originally accumulate after detachment from the neuroepithelium of the utricular macula secondary to a type of degeneration. An idiopathic form, which is assumed to occur spontaneously, is diagnosed when the causative pathology is obscure. However, an association between various other systemic or inner ear conditions and BPPV has been reported, indicating the existence of secondary BPPV. This study was performed to present the first review of the pathology underlying BPPV following a complete PubMed/Medline search. In total, 1932 articles published from 1975 to 2018 were reviewed. The articles were classified according to 17 potentially causative factors (aging; migraine; Meniere's disease; infection; trauma; idiopathic sudden sensorineural hearing loss; sleeping habits; osteoporosis and vitamin D insufficiency; hyperglycemia and diabetes mellitus; chronic head and neck pain; vestibule or semicircular canal pathology; pigmentation disorders; estrogen deficiency; neurological disorders; autoimmune, inflammatory, or rheumatologic disorders; familial or genetic predisposition; and allergy). A discussion of the underlying cause of BPPV for each factor is presented.

## Keywords

Benign paroxysmal positional vertigo, aging, trauma, migraine, Meniere's disease, vestibular neuronitis, vitamin D deficiency

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## Introduction

Benign paroxysmal positional vertigo (BPPV) can be defined as transient, position-induced torsional, vertical, or horizontal nystagmus with vertigo. Symptoms

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are provoked in association with a specific head position. The diagnosis is supported by the brief latency, limited duration, fatigability, and reversibility of the nystagmus upon returning to an erect position. The pathology is based on displacement of the cupula due to either free-floating debris/otoliths in the semicircular canal (canalolithiasis) or attachment of debris/otoliths to the cupula (cupulolithiasis).

Any inner ear pathology that detaches the otoconia appears to be capable of causing BPPV. Secondary BPPV is diagnosed when an associated cause is clearly identified. However, the underlying pathology is often obscure; in such cases, idiopathic BPPV is diagnosed.<sup>1</sup> This study was performed to review the pathologies possibly underlying the occurrence of BPPV.

## **Review of the literature**

A review of the literature on the pathology underlying BPPV was conducted. The articles were identified by means of a search of the PubMed database using the keyword "BPPV," which yielded 1932 articles. The search included articles published from 1975 to 2018. In total, 545 articles were reviewed for the study after exclusion of those that were not published in English, those that were technical or guideline reports, those based on the outcomes of a specific treatment method or analysis of quality of life only, experimental studies that focused on a mathematical model of BPPV, and single case reports. Comparative studies were excluded if the discussion of the underlying pathology was not clear. If more than one article by the same author(s) or institution was found, only the most recent article matching the aforementioned criteria and those that were not overlapping were included.

Seventeen factors possibly associated with the pathology underlying BPPV were identified: aging; migraine; Meniere's

disease; trauma; infection and vestibular neuronitis; idiopathic sudden sensorineural hearing loss; sleeping habits; osteoporosis and vitamin D insufficiency; hyperglycemia and diabetes mellitus; chronic head and neck pain; vestibule or semicircular canal pathology; pigmentation disorders; estrogen deficiency; neurological disorders; autoimmune, inflammatory, or rheumatologic disorders; familial or genetic predisposition; and allergy.

## **Findings**

After searching articles regarding BPPV in older people, including reports focused on the aging of the labyrinth, 78 articles were selected. Forty-seven articles were about the association of migraine and BPPV; 56 were about Meniere's disease and BPPV; 37 were about viral infections and vestibular neuronitis, which may have a role in the pathogenesis of BPPV; 63 were about BPPV following trauma; 25 were about idiopathic sudden sensorineural hearing loss accompanying BPPV; 21 were about the role of sleeping habits in BPPV; 41 investigated the relationship among vitamin D levels, osteoporosis, and BPPV; 15 focused on the association among hyperglycemia, diabetes mellitus, and BPPV; 8 were about the relationship among myalgia, fibromyalgia, chronic neck pain, and BPPV; 18 investigated vascular or anatomical abnormalities, including a large vestibular aqueduct, Arnold-Chiari malformation, abnormalities in the vertebral and basilar arteries, hypoplasia of the semicircular canals, and other conditions that may have a role in the pathogenesis of BPPV; 2 were about the relationship between BPPV and pigmentation disorders; 5 were about estrogen deficiency in BPPV; 9 focused on the association of BPPV and neurological disease, including multiple sclerosis and Parkinson disease; 12 were about possible defects associated with autoimmunity in patients with BPPV;

and 4 were about the familial incidence and possible genetic role in the pathogenesis of BPPV. No article addressed the association between BPPV and allergy. The distribution of these articles about the pathogenesis of BPPV is shown in Figure 1.

## Discussion

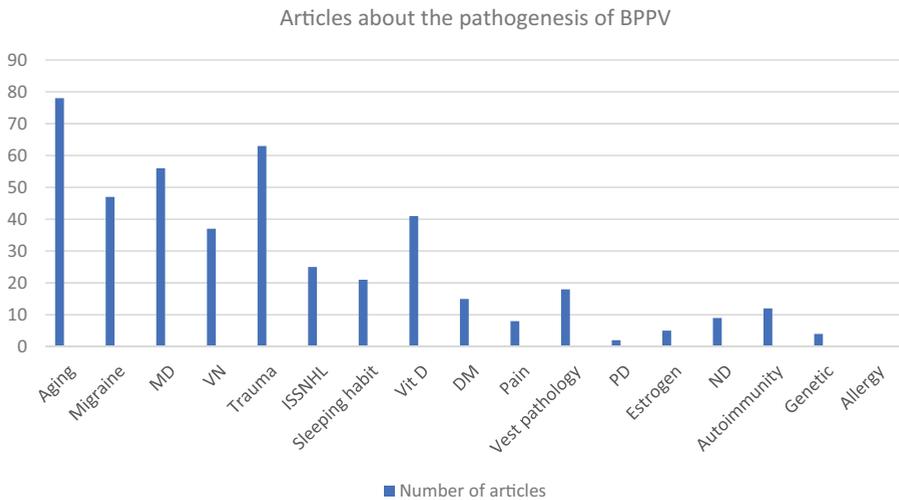
### Aging

Aging is a risk factor for utricular dysfunction in idiopathic BPPV.<sup>2</sup> Animal studies have indicated the occurrence of otoconial degeneration with aging.<sup>3,4</sup> The incidence of BPPV is higher at advanced ages, and it has been rarely reported to occur in children. Picciotti et al.<sup>5</sup> reviewed 475 patients with BPPV and found that comorbidities were present in 72.6% of patients with recurrent BPPV, and this incidence was higher in female and older patients. Yetiser and Ince<sup>6</sup> reviewed the age distribution of 263 patients from 10 to 84 years of age and found that 5 patients were younger than 20 years. Bachor et al.<sup>3</sup> reviewed 186

temporal bones from 121 individuals between the ages of newborn and 10 years. They found that the incidence of basophilic cupular deposits, which have been clinically implicated in BPPV, was 12.7%. The lower occurrence in children than adults suggested that the accumulation of deposits could be due to aging of the vestibular labyrinth. The average age at onset of the first episode of BPPV is >50 years. Residual symptoms such as dizziness and balance disorders are more common after otolith repositioning in older patients, and the recurrence rate is high.<sup>2,4</sup> This is probably because of otoconia fragmentation secondary to aging. Notably, however, this process is multifactorial.

### Migraine

Previous studies have shown that patients with migraine seem more likely to develop BPPV than subjects in the control group.<sup>7-9</sup> Kim et al.<sup>10</sup> performed a nationwide cohort study and reported a higher incidence of BPPV in patients with migraine (6.0%)



**Figure 1.** Distribution of articles focusing on the pathogenesis of BPPV. BPPV, benign paroxysmal positional vertigo; MD, Meniere’s disease; VN, vestibular neuronitis; ISSHL, idiopathic sudden sensorineural hearing loss; Vit D, vitamin D deficiency; PD, pigmentation disorder; ND, neurological disorder.

than in control subjects (3.2%). Faralli et al.<sup>11</sup> reviewed the recovery time, residual dizziness, and recurrence in patients with BPPV with and without migraine. The authors found no significant difference in the number of maneuvers needed to achieve recovery, and they stated that a direct pathophysiological link between migraine and BPPV is unlikely.<sup>11</sup> Yetiser and Gokmen<sup>12</sup> analyzed whether clinical features in patients with BPPV and migraine differ from those in patients with BPPV without migraine. The comparative analysis of the cure rate of the therapeutic maneuvers between the two groups showed no significant differences.

### *Meniere's disease*

Several reports have indicated an association between Meniere's disease and BPPV. The incidence greatly varies from 0.5% to 44.0%.<sup>1,13-15</sup> Meniere's disease and BPPV may share common pathological ground because of the high incidence of Meniere's disease and BPPV in the same ear.<sup>16-18</sup> Hydropically induced damage to the maculae of the utricle and saccule or partial obstruction of the membranous labyrinth are possible mechanisms underlying the coexistence of Meniere's disease and BPPV.<sup>19-21</sup> Several studies have shown that when BPPV is associated with Meniere's disease, more therapeutic sessions are needed and the recurrence rate is high.<sup>16,17,22,23</sup>

### *Infection and vestibular neuronitis*

Viral infections may play a role in the pathogenesis of BPPV. The occurrence of BPPV following vestibular neuronitis is not rare.<sup>24,25</sup> Hanci et al.<sup>26</sup> reported higher serological values for herpesvirus, Epstein-Barr virus, adenovirus, and cytomegalovirus in patients with BPPV than in the control group. BPPV secondary to

vestibular neuronitis is associated with a lower age at onset, more frequent involvement of the posterior canal, greater presence of canal weakness, and higher rate of recurrence.<sup>27</sup> Arbusow et al.<sup>28</sup> isolated herpes simplex virus in the labyrinth of 48% of studied temporal bones. However, the occurrence of infection-related otocorial detachment needs histopathological confirmation in animal studies.

### *Trauma*

Trauma is a common cause of BPPV. Pisani et al.<sup>29</sup> reviewed 3060 patients with a clinical diagnosis of BPPV, and a clear association with a traumatic event was present in 23.4% of patients. Chang et al.<sup>30</sup> reviewed 768 patients with BPPV and found that 9.2% of patients with BPPV had undergone previous dental surgery. Gordon et al.<sup>31</sup> followed the training program of 63 American football players and reported 16 additional cases of BPPV during follow-up. The most common types of trauma were motor vehicle crashes, common falls, temporal bone or stapes surgery, and head trauma.<sup>32-35</sup> Acoustic or electrical stimulation, pressure, intense physical activity, and mechanical trauma can lead to otoconial dislodgement.<sup>36-38</sup> Traumatic BPPV may involve multiple canals and requires repeated maneuvers.<sup>32,39-41</sup>

### *Idiopathic sudden sensorineural hearing loss*

Idiopathic sudden sensorineural hearing loss may accompany BPPV. The incidence of BPPV among patients with sudden hearing loss ranges from 5.4% to 12.1%.<sup>42-44</sup> Karlberg et al.<sup>45</sup> reported four cases of sudden hearing loss and ipsilateral posterior canal BPPV, all of which were resolved following a repositioning maneuver. The findings indicated that the pathology was located inside the labyrinth rather than

within the cochleovestibular nerve. Based on these cases, the authors proposed viral labyrinthitis rather than a vascular infarct. Conversely, El-Saied et al.<sup>46</sup> described five patients with hearing loss and BPPV and proposed a vascular insult as the common pathophysiological mechanism.<sup>46</sup> It seems that when BPPV is associated with sudden hearing loss, treatment requires several sessions of a repositioning maneuver.<sup>43,44</sup> Lee and Ban<sup>47</sup> reviewed 38 patients with sudden hearing loss and BPPV and proposed that the association of these two pathologies represents definite vestibular damage and is closely related to a poor prognosis.

### *Sleeping habits*

Gyo<sup>48</sup> was one of the first to indicate the occurrence of BPPV in a group of patients following bedrest restrictions after unrelated surgeries. Sleeping habits may be closely associated with the affected side in patients with BPPV. The ear affected by BPPV has been found to be consistent with the head-lying side.<sup>49,50</sup> Sato et al.<sup>51</sup> and Shim et al.<sup>52</sup> reported that otoconial debris dislodged from the utricle under the influence of gravity may fall into the lateral or posterior semicircular canals of the undermost ear during sleep. This is seen particularly more often in patients with posterior canal BPPV when the affected ear is down.<sup>53</sup> The recurrence rate is high when the patient continues to sleep on the affected side.<sup>54</sup> Sleeping habits may therefore be associated with hearing loss. Patients with profound unilateral hearing loss often lie on the ear with hearing loss while sleeping to keep the better-hearing ear open to the environment.

### *Osteoporosis and vitamin D insufficiency*

Research on the relationship between vitamin D levels and BPPV is evolving. Otoconia consist of calcium carbonate

crystals, which are connected to saccular and utricular hair cells with protein fibers. Vitamin D receptors regulate transportation of calcium through epithelial channels.<sup>55</sup> Therefore, vitamin D deficiency may affect the otoconia structure and integrity. The prevalence of a decreased bone mass density among people with BPPV is 81%.<sup>56</sup> A low serum vitamin D level is a risk factor for BPPV.<sup>57</sup> Yamanaka et al.<sup>58</sup> found that the rate of recurrence of BPPV in patients with osteoporosis was significantly higher than that in patients with normal bone mineral density (56.3% vs. 16.1%, respectively). When the symptom severity and recurrence rate were compared between patients with BPPV who had vitamin D deficiency versus a normal serum vitamin level, patients with vitamin D deficiency were found to have more severe symptoms with a longer duration, a lower success rate of repositioning maneuvers, and a higher recurrence rate.<sup>59,60</sup> The vitamin D level is particularly low in postmenopausal women with BPPV.<sup>61</sup> A low vitamin D level is associated with osteoporosis, and medication to treat osteoporosis can provide protection against BPPV and reduce the incidence of recurrence.<sup>62,63</sup> Talaat et al.<sup>64</sup> reported that the rate of recurrence of BPPV in patients with an elevated serum vitamin D level following replacement therapy was quite low during the follow-up period (4%) when compared with that in patients with a low serum vitamin D level (43%).

### *Hyperglycemia and diabetes mellitus*

Disruption of capillary vessels causes microvascular degeneration leading to proximal and distal peripheral sensory and motor neuropathy in patients with chronic hyperglycemia and hyperinsulinemia. Yoda et al.<sup>65</sup> reviewed 28 temporal bones from 14 patients with type 1 diabetes mellitus and 56 normal temporal bones from 28 age-matched

individuals. The prevalence of cupular and free-floating deposits in the lateral and posterior semicircular canals was significantly higher in the patients with type 1 diabetes mellitus than in the patients with normal temporal bones, and this difference was associated with the duration of disease rather than with aging.<sup>65</sup> D'Silva et al.<sup>66</sup> reported that BPPV was seen 46% of patients with type 2 diabetes mellitus compared with 37% of individuals without diabetes mellitus, and the 42% association between type 2 diabetes mellitus and BPPV was mediated by hypertension. Hyperglycemia is also a risk factor for recurrence.<sup>67</sup>

### *Chronic head and neck pain*

Observational studies have indicated a connection between chronic BPPV and headache and neck pain.<sup>68</sup> Patients with pain benefit from otolith repositioning maneuvers.<sup>69</sup> Whether myalgia, fibromyalgia, and pain influence detachment of otoconia remains unclear because most such studies are observational and the results are based on self-scoring questionnaires. Whether neck pain is the cause or consequence of BPPV also remains unclear.

### *Vestibule or semicircular canal pathology*

BPPV is usually a self-limiting disease that responds well to repositioning maneuvers. Schratzenstaller et al.<sup>70</sup> reviewed the magnetic resonance images of patients with atypical and intractable BPPV. They found structural changes such as fractures or filling defects in the semicircular canals. Magnetic resonance imaging is helpful to understand micro-abnormalities of the semicircular canals in patients with persistent symptoms.<sup>71</sup> In contrast, no gross anatomical abnormalities were found in that study.<sup>70</sup> Recurrent BPPV is reportedly related to volumetric abnormalities of the vestibular aqueduct.<sup>72</sup> The incidence of

BPPV in patients with a large vestibular aqueduct is approximately 19%.<sup>73</sup> However, no evidence-based pathological mechanism was demonstrated.

### *Pigmentation disorders (vitiligo)*

Melanocytes arise from the neural crest and are found in the utricle, saccule, ampulla, and endolymphatic duct and sac. Impaired proliferation of these cells results with white patches of the skin known as vitiligo.<sup>74</sup> The role and presence of pigment cells in the inner ear are subject to investigation. Melanocytes are particularly present around capillary walls. They seem to have a vasomotor function and play a role in metabolite exchanges.<sup>75</sup> Vitiligo-associated auditory problems may be related to a degenerative process.<sup>76</sup> Dawoud et al.<sup>77</sup> reviewed 30 patients with vitiligo and reported that 17% had BPPV. However, it is difficult to conclude that pigmentation disorders are a cause of BPPV because of the lack of sufficient data.

### *Estrogen deficiency*

The prevalence of BPPV greatly increases with age in both sexes. However, menopausal women are especially susceptible. Decreases in estrogen and progesterone levels can cause inner ear microcirculation disorders in postmenopausal women.<sup>78</sup> Animal studies have indicated that estrogen receptors are important in otoconia maintenance. Bilateral ovariectomized mice have reduced expression of otoconial components. The density of otoconia decreases but the size of otoconia increases in female ovariectomized rats. Eventually, ectopic debris formation in the ampulla increases under estrogen deficiency.<sup>79,80</sup>

### *Neurological disorders*

BPPV has been reported in patients with multiple sclerosis and Parkinson's

disease.<sup>81,82</sup> The association between BPPV and neurological disorders is weak, and data on the pathophysiological mechanism connecting these two clinical disorders are lacking.<sup>83</sup> The occurrence of BPPV in patients with neurological disease seems to be coincidental.

### *Autoimmune, inflammatory, or rheumatologic disorders*

Possible defects associated with autoimmunity in patients with BPPV have been a topic of interest. However, conflicting results have been reported. The association of giant cell arteritis and BPPV has been reported in 20% of patients, suggesting an ischemic pattern of otoconia degeneration.<sup>84</sup> Goto et al.<sup>85</sup> reviewed reactive oxygen metabolites and circulating soluble vascular cell adhesion molecule to investigate the possible contributory role of angiitis to the onset of BPPV. The results were significant, suggesting alternative pharmacological treatment. Pérez et al.<sup>86</sup> reported successful intratympanic methylprednisolone treatment in seven of nine patients with persistent posterior canal BPPV. Amor-Dorado et al.<sup>87</sup> found that the incidence of BPPV among 59 patients with ankylosing spondylitis was low (10%). Modugno et al.<sup>88</sup> found anti-thyroid antibodies in 27% of patients with BPPV and proposed the existence of immune complex-mediated inner ear disease. However, another study showed no significant difference in the level of thyroid-stimulating hormone, anti-thyroid peroxidase antibody, or anti-thyroglobulin antibody between patients with and without BPPV.<sup>89</sup>

### *Familial incidence*

Gizzi et al.<sup>90</sup> reviewed the family histories of patients with BPPV, and the results suggested a genetic predisposition to utricular otoconia dislodgement. The authors

compared the familial tendencies between 120 successive patients with BPPV and 120 successive patients with dizziness. Patients with BPPV were five times more likely to have relatives with BPPV than were patients with dizziness (control group). However, no clear hereditary or environmental influence on the development of BPPV was found. Whether BPPV is inherited in an autosomal dominant fashion needs to be confirmed in further studies.<sup>91</sup>

### *Allergy*

No research focusing on the association between BPPV and allergy is available.

### **Conclusion**

This review has provided a discussion of some possible underlying causes of BPPV, although the idiopathic form is clearly the most common. Lee et al.<sup>92</sup> reviewed 718 patients with BPPV. Sixty-nine patients (9.6%) had inner ear disorders associated with BPPV, and the most common pathologies were sudden hearing loss, Meniere's disease, and vestibular neuronitis.<sup>92</sup> Further studies are required to explore clear links before presenting solid statements. Otoconial degeneration due to aging seems to be important. However, BPPV cannot be solely explained by aging. Secondary problems should be investigated before initiating the clinical decision-making process in patients with BPPV. The gravitational impact of the sleeping position is an interesting factor. Patients should be recommended to sleep on the healthy side following repositioning maneuvers; this is a minor but valuable precaution to reduce recurrence. Additionally, vitamin D and estrogen deficiency should be considered when treating postmenopausal women with BPPV. BPPV following trauma is usually clear in cases of surgery, head trauma, or vehicle accidents. Patients

should also be questioned regarding minor impacts. BPPV occurs in combination with many pathologic conditions. The present review has indicated that aging, trauma, migraine, Meniere's disease, and vestibular neuronitis are the most frequently investigated topics. However, studies of vitamin D deficiency have recently been increasing.

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