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Causes and treatment of idiopathic benign paroxysmal positional vertigo based on endocrinological and other metabolic factors

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ABSTRACT

The genesis of the Benign Paroxysmal Positional Vertigo (BPPV) seems to be related to some metabolic factors. These factors, such as vitamin D, glucocorticoids, and even thyroid and growth hormones, can affect bone metabolism and the mineralization of otoconia. It also seems to link to factors related to aging or nutritional habits. Besides, since the incidence of BPPV is quantitatively higher in women than in men, female sex steroids could be associated with this process. It could be useful to understand how these factors act in otoconial mineralization if we want to develop treatments aimed at preventing or delaying BPPV recurrences. In this review, we will analyze the role of these metabolic and hormonal factors in otoconial mineralization and in the treatment of BPPV.

Contents

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1. Introduction

The otolith organs, composed of the saccule and the utricle, detect head tilt or translational accelerations by gravity (Purves et al., 2001). These include a sensory epithelium (macula) where the calcium carbonate crystals rest (called otoconia or otoliths). They are essential elements to detect these cephalic movements. The release of otoliths and their action in the semicircular canals generate Benign Paroxysmal Positional Vertigo (BPPV), one of the most frequent vestibular disorders that can occur due to a migration of the otolith particles to one or several semicircular canals. The presence of adherent debris to the cupula can also produce this disorder (Purves et al., 2001; You et al., 2019).

The duration and type of nystagmus would help us identify the affected canal, and if it follows a pattern of canalolithiasis or cupulolithiasis. Epidemiologically, the BPPV can present different patterns related to sex, age, and the type of canal or ear affected. Although they share common clinical symptoms, with an intense and short sensation of torsional vertigo triggered by cephalic movements with a vegetative response, the etiology of BPPV is diverse. Trauma is the most common identifiable cause. However, in a significant percentage of cases, the origin of vertigo is unknown (You et al., 2019). There are two relevant, intimately related factors that trigger the appearance of this type of vertigo: age, due to vestibular degeneration, and female sex, due to hormonal factors, both involved in changes in bone metabolism (Liu et al., 2017). That is the reason why multiple metabolic causes have been proposed to explain the genesis of idiopathic BPPV, including certain eating habits, such as excessive consumption of carbohydrates and fats, or hypertension (D'Silva et al., 2016; Scultz et al., 2015; Ogun et al., 2014). Understanding how these factors act will allow us to propose possible treatments to correct these metabolic dysfunctions that could cope with the disease.

In this review, we will attempt to summarize these related causes and establish possible therapeutic options according to the different possible aetiologies, starting with a series of studies shown in Table 1.

2. Otoconial mineralization and BPPV

Otoconia formation involves different proteins. The most important is Otoconin-90, the matrix protein, which interacts with other minor calcium-binding proteins, such as otolin, osteopontin or cerebellin, which act as support (Andrade et al., 2012; Deans et al., 2010).

The presence of factors that affect these protein interactions, the calcium-binding process itself or the availability of this cation will result in an alteration of the otoconial mineralization process, which will cause a pathological situation. We will analyze these factors.

2.1. Aging

Aging harms the configuration of the otoconia since it favors the weakness or loss of the anchorage of the fibrils that interconnect the otoconia (Andrade et al., 2012). We observe this factor in animal models, such as elderly rats, in which the bodies of many otoconia have fissures, tears and fragments in both maculae due to the weakness of their binding filaments. Giant otoconia can appear in the outer margin of the utricular maculae (Jang et al., 2006). We attribute this effect to changes in ionic and acid-base balance. A decrease in pH results in a uniform reduction in the size of the otoconia, while the complex formation of calcium ions and changes in ion concentrations result in more selective alterations. Any of these changes facilitate otoconial degeneration and the creation of fragments and remains (Walther et al., 2014). These adverse effects that appear with aging can also be due to the lack of sex hormone production, typical of menopause and to the absence of GH secretion associated with aging, as we will analyze later (Devesa et al., 2016).

2.2. Hormones

Some hormones play a significant role in otoconial mineralization. The deficient production of these hormones can contribute significantly to the appearance of a pathological situation at the level of the otoconia.

2.2.1. Estrogens

We can deduce the role that estrogens can play in the otoconial mineralization process because type 2 estrogen receptor (ESR2) expresses both in the saccules and in the utricles (Yang et al., 2018a). Preclinical studies in rats undergoing bilateral ovariectomy show that these animals have significant imbalance disorders, objectified in the classic rotarod test. We can observe by electron microscopy in these ovariectomized rats an abnormal morphology of the otoconia in the utricular region, adjacent to the ampulla (Yang et al., 2018b). There is also a lack of expression or a reduction

Table 1
Summary of BPPV supplementary treatments performed in human patients. HRT: Hormonal replacement therapy.

Compound	Study	Results	Authors
Estrogen	A retrospective population study to analyze the incidence of BPPV and protective factors against it.	The incidence of BPPV is significantly lower in estrogen-treated patients due to menopausal syndromes.	Liu et al., (2017).
Estrogen + Progesterone	A prospective study of 10 female patients diagnosed with BPPV and treated with HRT.	The cessation of treatment with oral contraceptives keeps vertigo under control.	Giacomini et al., (2006).
Vitamin D	A longitudinal study of patients with low levels of vitamin D (<20 ng/mL), 27 treated/27 not treated with 50.000 IU cholecalciferol weekly + maneuvers for two months.	The group treated with vitamin D decreased BPPV episodes. They remained stable and unchanged during the study period compared to the untreated group.	Sheikhzadeh et al., (2016).
Vitamin D	A prospective study of 40 patients with BPPV; 16 out of them were treated with vitamin D due to their low levels (unspecified dose).	Supplementation decreased BPPV episodes, but the results were not statistically significant.	Cupido et al., (2018).
Bisphosphonates Raloxifene Calcitonin Teriparatide	A retrospective study of osteoporosis treated in 260 women with and BPPV, aged 51–80 years.	A negative association between BPPV and treated osteoporosis in women aged 51–60 years.	Mikulec et al., 2009.
Methylprednisolone	A pilot study of 9 patients with persistent posterior canal BPPV treated intratympanically (two weekly doses of 0.3–0.4 mg/mL to 40 mg/mL) before repeating repositioning procedures.	7 out of 9 patients were relieved of their symptoms and did not exhibit positional nystagmus after 1 or 2 repositioning maneuvers.	Perez et al., (2016).
Dexamethasone	2 cases with intractable posterior BPPV treated with 3.3 mg in 1 ml solution	Relief of symptoms and absence of nystagmus in positional maneuvers.	Kelkar et al., (2018).

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in Otoconin-90 and Otolin in these rats. Immunohistochemical studies show an increase in ectopic particles near the crista.

This observation agrees with the fact that the prevalence of BPPV is higher in women than in men, supporting the role that female sex steroids can play in the etiopathogenesis of this condition (Ogun et al., 2006). The decrease in circulating female sex hormones leads to disorders of the inner ear microcirculation that could explain the genesis of BPPV. Changes in female sex steroid levels can induce electrolyte, endolymphatic pH, calcium or lipid modifications. Menopausal women with BPPV have a more significant decrease in plasma levels of progesterone (up to 64.92%) and estrogen (33.18%) than in menopausal women without BPPV (Wang et al., 2017). Given the negative role that progesterone plays in the inner ear balance, estrogen deficiency seems to be the most critical factor involved in the development of BPPV. A prospective study conducted on 228 postmenopausal women found that women with possible evidence of BPPV showed that the incidence of real BPPV was higher in those patients with lower estrogen levels than in the control group matched in age, BMI, high blood pressure and diabetes (Yang et al., 2018b). Therefore, it is clear that estrogens play a decisive critical role in otoconial mineralization.

2.2.2. Thyroid hormones

The role of thyroid hormones (TH) in the regulation of otolithic organs has been extensively studied in fish models. TH regulates the growth of fish otoliths in the juvenile period, specifically T3, which presumably acts on the alpha thyroid receptor (Shiao and Hwang, 2004; Shiao et al., 2008). Conversely, the use of thyroid hormone inhibitors prevents the correct growth of vestibular structures, such as the saccule and utricle (Schreiber et al., 2010).

Thyroid disorders in humans may be associated with various diseases of the inner ear; that is why some studies attempted to link these disorders with BPPV (Coffin et al., 2012; Ogun et al., 2014). Autoimmunity seems to be the reason for a higher prevalence of vertigo. We can observe it in anti-thyroglobulin antibodies positive and anti-thyroperoxidase antibodies positive euthyroid subjects (Guerra and Devesa, 2019; Modugno et al., 2000). However, a later study could not replicate this result (Papi et al., 2010). Therefore, it is likely that thyroid autoimmunity is a risk factor for developing other disorders of the inner ear, such as autoimmune hearing loss or Meniere's disease (Fayyaz and Upreti, 2018; Sari et al., 2015).

2.2.3. Corticosteroids

There are corticosteroid receptors in the inner ear that appear to be involved in the development of this structure, but their role in otoconial morphogenesis is unknown (Pitovski et al., 1994; Rarey and Curtis, 1996). The effect of these hormones on bone metabolism is negative (Mitra, 2011), as shown by the appearance of osteoporosis in subjects chronically treated with these steroids. However, intratympanic or systemic administration of corticosteroids is a standard treatment to control the symptoms of several vertiginous syndromes, such as Meniere's disease or vestibular neuritis (Patel, 2017; Sjögren et al., 2019). It is because these hormones are anti-inflammatory and play a role in fluid and electrolyte regulation, therefore, improving homeostasis of the inner ear.

2.2.4. Growth hormone

The role of this hormone in bone metabolism is well known; therefore, it is likely that it plays a role in otoconia mineralization. Therapy with bovine GH on hypophysectomized fish counteracts the reduction in otoliths, and even exceeds their sham levels. Results suggest that GH plays an essential role in otolith calcification, possibly via matrix-related sequences. It indicates that GH plays a decisive role in the otolith mineralization (Shinobu and Mugiya, 1995). However, we need to carry out further studies for a better understanding of the mechanism of action of GH at this level, because there is no research on humans so far.

2.2.5. Vitamin D

Although it has been considered classically as a vitamin, it is a real hormone that plays multiple vital functions in the body. Vitamin D receptor (VDR) expresses in mice in the crista ampullaris of the semicircular membranous canals, and the surrounding osteocytes. Preclinical studies in VDR knockout mice indicate that these animals suffer from vestibular dysfunction with a lower expression of these structures. The saccular and utricular maculae, as well as the crista ampullaris, are morphologically normal without alterations in the stereociliary structure (Minasyan et al., 2009).

Many patients with idiopathic BPPV may show decreased vitamin D plasma levels, and the recurrences are independent of the initially affected ear (Talaat et al., 2016). This condition occurs both in states of vitamin D insufficiency (<20 ng/mL) and the deficiency (<10 ng/mL) and they are independent of age, sex, BMI, metabolic diseases, and estrogen levels. Therefore, it is hypothesized that maintaining low levels of vitamin D may increase the risk of recurrence of this vertigo, since a lack of vitamin D may affect the structure and integrity of otoconia. In patients over 70, there is a negative correlation between high levels of Otolin-1, a marker of otolithic degeneration, and plasma levels of vitamin D (Parham et al., 2018). However, vitamin D deficiency states are standard in the general population, up to 60% of them suffer from it. Therefore, some reports have not been able to establish a causal relationship (Jeong et al., 2013). Although there are studies with controversial results in developing a linear relationship between vitamin D and recurrences (Karataş et al., 2017), there is significant evidence when comparing groups with low plasma levels of this vitamin (Ding et al., 2019; Rhim, 2019). Lower plasma levels of vitamin D in patients with canalolithiasis compared to those with cupulolithiasis have been reported in subjects diagnosed with posterior canal BPPV (Maslovara et al., 2018), a result confirmed in a subsequent study in a group of patients with horizontal canal involvement (Nakada et al., 2019). A recent meta-analysis showed that, although low vitamin D levels increase the risk of BPPV recurrences, we cannot establish a link between the risk of BPPV and low vitamin D levels (AlGarni et al., 2018).

2.3. Drugs and treatments for other diseases

If we base on the roles that the factors mentioned above play on the mineralization of the otoconia, it is only logical that specific treatments affecting one or more of these factors can also affect mineralization. Therefore, they contribute to the appearance of BPPV. It is the case, for example, of osteoporosis treatments.

The prevalence of BPPV in patients with osteoporosis is higher than in the general population (Yu et al., 2014). A nationwide population-based cohort study of 177,797 subjects showed a higher risk of recurrence of 1.15 times higher than in subjects without osteoporosis (Byun et al., 2019). Previous studies had confirmed these findings in the population at risk (26% of patients with osteoporosis confirmed by bone densitometry). Also, recurrence in osteoporotic patients is higher than in controls (56.3% versus 16.1%). As mentioned above, the reason for this increased risk seems to be related to the regulatory role that estrogens play in calcium metabolism for otolith mineralization, but also due to osteopontin expression and the function of CaCO3 (Yamanaka et al., 2013). This risk increases especially in patients with canalolithiasis (Vibert et al., 2003). The reason for this increased risk is unknown; we assume that there are different pathophysiological mechanisms responsible for the development of canalolithiasis and cupulolithiasis. Ten years ago, a study tried to clarify whether some treatments for

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Table 2
Treatments proposed for recurrent BPPV based on hormones and other factors.

Estrogens	Lesser episodes of vertigo in women who need estrogen hormone replacement therapy. Not recommended to treat the recurrence of positional vertigo exclusively. Consider the short-term use of phytoestrogens in women with low estrogen levels.
Vitamin D	Use in population with recurrent vertigo and low levels of vitamin D. Given the safety of this treatment, as well as the high prevalence of this vitamin deficit, it is pending to evaluate in new studies its standardized use in the entire population.
Osteoporosis Treatment	Fewer recurrences in patients with vertigo and osteoporosis. Standardized use not recommended.
Corticosteroids	Approach treatment with caution. Use the intratympanic injection technique once confirmed positional vertigo and other therapeutic options had been ruled out.
Thyroid hormones	Not recommended given the association of BPPV with autoimmunity, not with metabolic disorders of the thyroid itself.
Growth Hormone	Although it regulates bone metabolism, studies with human patients are needed.

osteoporosis could reduce the risk of vertigo recurrence (Mikulec et al., 2010). They carried out the research in women treated with bisphosphonates, raloxifene, calcitonin or teriparatide, excluding patients treated with hormone replacement therapy or calcium. The results obtained showed a negative relationship between BPPV and treated osteoporosis in women aged between 51 and 60 years. However, no significant effects were found among the older age groups or for the group in general. Other studies observed a spurious or weak association in this regard (Minasyan et al., 2009).

Despite the role that, in general, calcium plays in mineralization, the attempts made trying to link the low levels of this cation with the development of BPPV have not proved significant (Hoyos et al., 2017; Wang et al., 2017).

3. Potential treatments for preventing BPPV recurrences

3.1. Estrogens

The increased risk of vertigo in menopausal women seems to decrease with oral estrogen intake for menopause symptoms, according to a large national population study performed in Taiwan (Liu et al., 2017). On the other hand, another report showed that treatment with combined hormone replacement therapy seems to increase BPPV recurrences, and when treatment is discontinued, women reduce symptoms (Giacomini et al., 2006). However, this study was limited by the low number of patients involved (10 subjects), the absence of a control group and the early interruption of treatment that could explain spontaneous recovery regardless of treatment. As mentioned earlier, this effect could be explained by a potentially harmful role exerted by progesterone and not by estrogens.

There is a lower incidence of hair cell death in rats treated with 17-estradiol, expressing otoconin-90, and phytoestrogen supplementation improves otoconial morphology (Yang et al., 2018a). It is not still demonstrated whether phytoestrogen supplementation would diminish recurrences in humans, although results for controlling menopausal symptoms are controversial (Chen et al., 2014).

3.2. Vitamin D

A study carried out in patients with recurrent vertigo, in which one group was treated with particle repositioning maneuver; another group was treated with similar procedures plus vitamin D (50,000 IU per week for 2 months); and a third group received no treatment at all, with a 6-month follow-up period, showed that the first two groups experienced an apparent decrease in episodes of vertigo, being more significant in the group that received vitamin D, while no improvements were observed in untreated patients (Sheikhzadeh et al., 2016). A subsequent study performed in a group treated with the vitamin confirmed these findings after a 6-month follow-up period, but in this case, the results obtained were not statistically significant (Cupido et al., 2018).

3.3. Thyroid hormones

It has not been observed to date whether thyroid hormone treatment could manage BPPV recurrences, either in deficiency of these hormones or excess situations. However, in animal models, the use of exogenous thyroid hormones is involved in the crystallization of otoliths, modifying their morphology and composition (Santosh and Rao, 2016).

3.4. Corticosteroids

In many patients, BPPV coexists with other associated vertiginous syndromes, such as vestibular migraine, Meniere's disease or vestibular neuritis (You et al., 2019). However, few studies have proposed a corticosteroid treatment in BPPV. An interesting study carried out in a small group of patients who suffered unilateral vertigo of the posterior refractory semicircular canal that failed after particle repositioning maneuvers, showed that two sessions of intratympanic methylprednisolone injections, combined with therapeutic maneuvers, led to symptom relief and the absence of recurrences in 78% of patients (Pérez et al., 2016). A subsequent publication with two similar cases treated with dexamethasone obtained the same results (Kelkar and Johnson, 2018). Although these results are promising, more studies are needed, and we should not ignore that, although ordinarily safe, this type of treatment involves an invasive approach. This effectiveness is paradoxical, given the effect of corticosteroids on bone metabolism (Mitra, 2011).

3.5. Growth hormone

The genesis of vertigo involves multiple neurotransmitters and hormones that modulate its clinical expression. Under physiological conditions, the vestibular system influences the secretion of different neurohormones, including GH. It is because vestibular stimulation induces stimulation of the ipsilateral vagus nerve, but not that of the same nerve contralateral to stimulation (Sailesh and Mukkadan, 2014). As is well known, vagal stimulation induces GH secretion mediated by the increase in acetylcholine. There are no studies to date, indicating that the administration of GH may be useful in the treatment of BPPV. Still, given the described actions of this hormone on the mineralization of otolith (Shinobu and Mugiya, 1995) and its known effects on bone metabolism (Devesa et al., 2016), it is feasible to think that, in situations of GH deficiency, as physiologically occurs in old age, its administration may be of utility in the treatment of BPPV.

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4. Conclusions

Treatment proposals for BPPV recurrences are summarized in Table 2. As noted earlier, the role of different hormonal factors involved in bone metabolism for the development of otoconia is undeniable. Although the role of hormonal and metabolic factors in the genesis of BPPV is evident, there are only a few preliminary and limited studies in humans that evaluate the impact of treating these factors to reduce recurrences. Vitamin D supplementation is undoubtedly the most recommended option due to its low side effects and the low plasma levels of this vitamin that are generally found in the world population. Other medications, such as corticosteroids, phytoestrogens or even GH, may be an option. Still, we need to carry out studies to validate and establish treatment protocols with any of these.

Declaration of cpeting interestCOI

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