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Is hypovitaminosis D a risk factor for either the onset or the recurrence of Benign Paroxysmal Positional Vertigo?

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Abstract

Aims of the study. To check if: 1. There is an association between serum levels of vitamin D and BPPV; 2. There is a seasonality of BPVV; 3. Serum levels of 25-OH vitamin D of the BPPV patients are significantly different if compared to a healthy control group homogeneous by gender and age; 4. Patients with > 3 episodes of BPPV in the previous 12 months presented 25-OH vitamin D levels significantly different if compared to the patients with < 3 episodes of BPPV during the same period; 5. In case of hypovitaminosis D, the supplementation of vitamin D3 reduced the recurrence rate of BPPV in a one-year follow-up.

Patients and Methods. From December 2015 to February 2016, 68 patients affected by non- traumatic BPPV and a homogeneous control group of 50 individuals were included in the study; from June 2015 to August 2015 we included in the study other 59 BPPV patients and another homogeneous control group of 50 individuals, none of them included in the study during the previous period. In both patient groups and control groups the dosage of 25-OH vitamin D was performed. In all the cases of hypovitaminosis D, an oral supplementation of vitamin D3 was prescribed.

Results. In the winter period, both the patient group and the control group presented hypovitaminosis D very frequently -86.8% and 88%, respectively-, with no significant difference between them; the mean value of 25-OH vitamin D was significantly lower in the subgroup of BPPV patients with > 3 acute episodes in the previous year. In the summer period, hypovitaminosis D was less frequent in both the groups- 61% and 62% respectively- whereas the frequency of BPPV seems to be not different respect the winter period.

Conclusions. Hypovitaminosis D is a major health problem in our community. It is not related to a higher incidence of BPPV, whereas the lowest values of 25-OH vitamin D are related to the highest incidence of recurrences. In a one year follow up, the supplementation of vitamin D3 was able to reduce the number of BPPV recurrences.

Introduction

Benign Paroxysmal Positional Vertigo (BPPV) represents more than 20% of all vertiginous syndromes [1,2]. It is usually caused by free-floating otoconia dislodged from the utricle in the semicircular canals (canalolithiasis) or by otoconia adherent to the cupula of a semicircular canal (cupulolithiasis). Posterior canal is involved in 75-85% of the cases; lateral canal is involved in 15-20%, whereas anterior canalolithiasis is the rarest form (2-3%) [3].

BPPV is characterized by recurrent short-lasting episodes of vertigo when the patient changes his/her position; the critical period usually lasts from few days to one month, seldom its duration is longer. Diagnosis is based on the presence of positional and paroxysmal nystagmus evoked through the Dix-Hallpike diagnostic test for vertical

canals BPPV [4], as well as through the Pagnini–McClure test (Head-rolling test) for lateral canal BPPV [5,6]. Nystagmus is rotatory with linear upward or downward component for the vertical canal BPPV, horizontal, geotropic or apogeotropic, for the lateral canal BPPV. BPPV is more frequent in the elderly, with a maximum incidence in people > 60 years; it is rare in the younger age and very rare in the childhood [7]. Its frequency is considered a common cause of falling [8], with increased risk of fractures [9] in the elderly. A recent cranial trauma is considered the only certain cause, whereas diabetes, hypotension, autoimmunity, migraine, or other ear diseases (chronic otitis media, otosclerosis, and Menière's disease) are only putative causes or facilitating factors [3]. Otoconia have a glycoproteic central core with a low level of calcium and a peripheral zone with a higher level of calcium carbonate [10]. Connections between osteoporosis and

BPPV were hypothesized in 2003 [11] and proposed again by Jeong in 2009 [12] and Kim in 2016 [13]. A relationship between 25-OH vitamin D serum levels and BPPV has been hypothesized by some Authors [14-16].

Aims of the study. Check if: 1. There is an association between serum levels of 25-OH vitamin D and BPPV; 2. there is a seasonality of BPVV, comparing the number of BPPV observed from November 2015 to February 2016 to those observed from June 2016 to August 2016. 3. Serum levels of 25-OH vitamin D of the population with BPPV are significantly different if compared to a population homogeneous by gender and age, suffering neither from audiological and vestibular disorders nor from calcium metabolism

disorders; 4. patients with three or more episodes of BPPV in the previous 12 months-from December 2014 to November 2015- presented 25-OH vitamin D serum levels

significantly different if compared to the control population and to the patients with less than three episodes of BPPV during the same period; 5. In a one year follow-up, the supplementation of vitamin D reduces the recurrence rate of BPPV.

Interventions. 1. BPPV treatment through a repositioning maneuver. 2. Vitamin D supplementation in cases of hypovitaminosis.

Patients and methods. From December 2015 to February 2016, a seasonal period in which the values of 25-OH vitamin D are uniform [17], 68 patients, 40 women and 28 men, mean age 60.2 +/- 12.41 years, affected by non-traumatic posterior or lateral canal BPPV, and without other otologic diseases, were included in the study. In the 12 months preceding the observation, a subgroup of 16 patients -10 women, 6 men, mean age 62.4 +/- 10.65 years, not significantly different compared to the whole BPPV group (p=0.5) and to the subgroup of 52 patients with less than three episodes of BPPV (p=0.4) – had experienced at least three episodes of BPPV; 12 patients had presented two episodes of BPPV, 40 patients just one episode. As an accessory part of the study, from June 2016 to August 2016 we included in the study other 59 patients- 36 women and 23 men-, mean age 59.7 +/- 10.41 years, none of them included in the study during the previous period, affected by non-traumatic posterior or lateral canal BPPV, and without other otologic diseases, to compare the frequency of BPPV in a period of low values of 25-OH vitamin D (December-February) with its frequency during a period with probably higher values of 25-OH vitamin D (June-August) [17,18]. The 25-OH vitamin D dosage was also performed in the same periods in the same laboratory in two homogeneous groups of respectively 50 subjects, 29 females and 21 males, mean age 60.3 +/- 11.27 years (p=0.9) from December 2015 to February 2016, and of 50 subjects, 31 females and 19 males, mean age 60.9 +/- 10.27 years (p=0.95) from June 2016 to August 2016, both suffering neither from audiological and vestibular diseases nor from calcium metabolism diseases. The 25-OH vitamin D dosage was dosed by chemioluminescence in the same laboratory in all the patients, always within 8.00 and 9.00 a.m. to minimize a possible circadian rhythm effect. Its values were grouped into: deficiency (< 10 ng / ml); insufficiency (11-30 ng / ml); normality (31-100 ng/ml); toxicity (> 100 ng / ml) [18,19]. In absence of contraindications to the use of vitamin D, we prescribed vitamin D supplementation in all the cases of hy-

povitaminosis, both in patients with BPPV and in the population-control. We used cholecalciferol (vitamin D3) per os, from 10.000 to 50.000 IU, weekly, in relation to the laboratory data, with the overall limit of 600.000 IU in a year.

A one year follow-up was conducted for the "winter patients" to observe if the supplementation of vitamin D3 reduced the recurrence rate of BPPV in the most frequently relapsing BPPV patients – 3 or more recurrences during the previous year-. For this purpose, patients were invited to a new visit in case of onset of symptoms related to a possible positional vertigo.

The statistical analysis was performed with the unpaired t-test (comparison of the values of 25-OH vitamin D and of the age in the various groups), Fisher's exact test (comparison between the incidence of functional classes of the value of 25-OH vitamin D in the different groups) and Grubbs' test to detect outliers in both the BPPV population and the control group.

Results. A. "*Winter cases*". In the BPPV group, hypovitaminosis D was found in 59/68 cases (86.8%) -deficiency in 25/68 cases (36.8%); insufficiency in 34/68 cases (50%)-; a normal value in 9/68 cases (13.2%). The mean value of 25-OH vitamin D was 18.2 +/- 10.43 ng/ml, with the presence of one outlier with a value of 58 ng/ml. In the subpopulation of 16 patients with at least three episodes of BPPV during the

previous 12 months, we found either a deficiency -10 cases- or an insufficiency -6 cases-of 25-OH vitamin D, with a mean value of 11.63 +/- 6.16 ng/ml vs. 20.38 +/- 10.73 ng/ml in

the group of BPPV patients with less than three acute episodes during the same period. The difference is statistically significant (p=0.003).

In the control group, hypovitaminosis D was found in 44/50 cases (88%) - deficiency in 17/50 cases (34%), insufficiency in 27/50 cases (54%)-, a normal value in 6/50 cases (12%).

The difference of hypovitaminosis D frequency between the two groups is not significant (p = 0.9). The mean value of 25-OH vitamin D in the control group was 15.61 +/- 9.87 ng /ml, with no outlier. The difference with the BPPV group was not significant (p = 0.21).The mean value of the control group is even significantly lower than that of the subgroup of 52 BPPV patients not frequently relapsing (p= 0.03).

B. "Summer cases". In the BPPV group, hypovitaminosis D was found in 36/59 cases (61%) -deficiency in 5/59 cases (8.4%); insufficiency in 31/59 cases (52.5%)-, a normal value in 23/59 cases (39%). The mean value of 25-OH vitamin D was 24.4 +/- 10.69 ng/ml, with the presence of one outlier (67 ng/ml).

In the control group, hypovitaminosis D was found in 31/50 cases (62%) - deficiency in 5/50 cases (10%), insufficiency in 26/50 cases (52%) -, a normal value in 19/50 cases (38%). The mean value of 25-OH vitamin D in the control group was 25.6 +/- 10.45 ng /ml, with the presence of one outlier (78 ng/ml). Differences with the BPPV group were not significant -p=0.16 for the mean value of vitamin D and p=0.8 for the frequency of hypovitaminosis-.

The cases of BPPV observed during winter and summer periods were similar (68 vs.59),; the ratio respect to the overall vestibular examinations of our Center was respectively 23.4% and 24.1%.

Differences of both 25-OH vitamin D values and incidence of hypovitaminosis D during winter and summer were significant, either in the BPPV groups (p=0.02; p=0.007) and in the control groups (p= 0.03; p=0.001), with a higher mean value of 25-OH vitamin D and a lower incidence of hypovitaminosis during the summer period.

One year follow-up from the beginning of the supplementation of vitamin D3. During the previous year we had observed 74 recurrences, 62 from the more frequently relapsing subgroup (16 patients, all with hypovitaminosis D), 12 from the less frequently relapsing subgroup (12 patients, 10 with hypovitaminosis D). After the oral supplementation of vitamin D3 in all the cases of hypovitaminosis, during the one year follow-up we observed 14 recurrences in

13 patients, 7 in the most frequently relapsing subgroup (two recurrences occurred in the same patient), 3 in the less frequently relapsing subgroup, 4 in the previously not relapsing patients. At the moment of the recurrence, the 25-OH vitamin D value was normal in 10 cases (> 30 ng/ml), low in 3 patients (< 20 ng/ml). The number of the observed recurrences was significantly lower than their expected number ($p<0.001$).

Discussion. Otoconia have a calcic inorganic part, so it is likely that their metabolism is influenced by the vitamin D levels. Vitamin D is implicated in calcium metabolism and in particular in calcium ligand proteins up-regulation; as shown in animal models, its action is also realized in the inner ear, where vitamin D receptors are expressed [17]. 25-OH vitamin D serum concentration is considered the best clinical indicator of bioavailable vitamin D reserves, with a threshold value for hypovitaminosis placed to 30 ng/ml [18,19]. Various studies have found a relationship between the levels of 25-OH vitamin D and bone mineral densities [20], risk of falls and fractures, cardiovascular events, cancer (especially colon, breast and prostate), depressive syndromes, diabetes, multiple sclerosis and others [21]. The vitamin D serum levels are variable during the year in relation to solar radiation exposure, with progressive lowering of its values from September to March, when the minimum peak is reached [22]. The frequency of hypovitaminosis D increases with age; in different geographic areas the 25-OH vitamin D values are frequently below the threshold value of hypovitaminosis (30 ng/ml) [15,19], with increment of all the risks associated with hypovitaminosis D (rickets, bone demineralization, neuromuscular impairment, falls and fractures). Most of the Italian elderly population who does not take oral supplements of vitamin D presents hypovitaminosis, but in Italy vitamin D insufficiency also affects about 50% of young people in the winter months [19, 23-25]. Hypovitaminosis D seems to be a major health problem, especially in the elderly. In fact, the supplementation of vitamin D is recommended to reach a target range of at least 30-40 ng / ml [15,19].

In 2003 Vibert [11] detected a significant association between osteoporosis and BPPV in 32 women. He proposed two possible mechanisms: the estrogen level decrease may cause a structural alteration of otoconia worsening their adhesion to the gelatinous matrix; the increase of free calcium in endolymph reduces the normal reabsorption of free-floating otoconia in the semicircular canals. A successive study by Walther confirmed the last mechanism [26]. In 2009 Jeong [12] showed a relationship between Bone-Mineral Density and BPPV in both men and women; more recently [14-16] a possible relationship between 25-OH vitamin D serum values and BPPV was shown.

In our study, in 68 patients with BPPV and in 50 healthy individuals not suffering from audiological, vestibular and neurological diseases, on the whole, hypovitaminosis D was found in 103/118 cases (87.3%) -deficiency in 42/118 cases (35.6%) and insufficiency in 61/118 cases (51.7%)-; the mean value of 25-OH vitamin D of 17.1 ng/ml was below the recommended minimum value of 30 ng/ml. This situation, independently from BPPV, seems in and of itself a major health problem, at least in our geographical area -Southern Italy, Sannio- and in the winter time.

Comparing the control group and the BPPV group, there were no significant differences both in the distribution of the conditions of deficiency and insufficiency (respectively 42/50 and 61/68 in the control group and in the BPPV group, $p=0.9$), and in the mean 25-OH vitamin D value (15.61 ng/ml in the control group vs.18.2 ng/ml in the BPPV group, $p = 0.21$). The mean value in the control group is even significantly lower than in the subgroup of BPPV with less than three relapses in the last year ($p=0.03$). Subdividing the BPPV group into two subgroups -52 patients with less than three episodes of BPPV in the last year and 16 patients with three or more episodes of BPPV in the same period- it has to be noted that in the more frequently relapsing patients, insufficiency (10 cases) and deficiency (6 cases) were always found, with a mean value of 25-OH vitamin D significantly lower respect to the subgroup of BPPV patients less frequently relapsing ($p= 0.003$). During the Summer period (from June to August) the mean value of vitamin D was significantly higher than the mean value observed during the Winter period, and the incidence of hy-

povitaminosis D was lower than in Winter, but the overall mean value of 25-OH vitamin D in 59 patients and in 50 healthy subjects was anyway below the recommended threshold of 30 ng/ml, whereas the observed frequency of BPPV was similar to that of the Winter period.

Our data highlighted that hypovitaminosis D, both as frequency and as mean value of 25-OH vitamin D, is not a factor risk for BPPV onset, but it is correlated with the increase of the frequency of relapses, with serum values of 25-OH vitamin D significantly lower in the more frequently relapsing subgroup.

All patients with BPPV were invited to a new visit in every case of recurrence of a positional vertigo, in order to assess during the year after the insertion in the study the frequency of BPPV recurrences and the 25-OH-vitamin D levels after its supplementation. Our results show a significant reduction of the number of recurrences either in the most frequently relapsing subgroup and in the less frequently or not previously relapsing subgroup, as other Authors reported [11,27], whereas the supplementation of vitamin D3 was able to correct hypovitaminosis in 10/13 patients again observed because a recurrence of BPPV.

Conclusions

1. In a Southern Italy area –Sannio-, during the winter time, hypovitaminosis D is a critical health problem, as other authors demonstrated even in different areas [14-16,18].

2. Our data confirmed the increase of vitamin D values in the summer.

2. Hypovitaminosis D, as an isolated factor, does not increase the frequency of BPPV onset.

3. Hypovitaminosis D appears to be significantly associated to the increase of the frequency of multiple recurrences of BPPV, regardless of sex and age.

4. Vitamin D3 supplementation, as well as it corrects the hypovitaminosis D, takes effect in reducing BPPV recurrences.

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