



Otoconial loss or lack of otoconia – An overlooked or ignored diagnosis of balance deficits

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ABSTRACT

Hypothesis: Lack of otoconia or otoconial loss may be the major reason for increasing imbalance with age, posttraumatic dizziness and residual dizziness as well as other so far unexplained imbalance affecting probably millions of people.

Background: It is written in every textbook that we need sensation of gravity for stable gait and stance, especially on two legs. Lack of otoconia is known to cause lifelong balance problems in animals. Loss of otoconia is happening in aging humans, like shown by increasing incidence of benign paroxysmal positional vertigo (BPPV) and in histological sections. While hundreds of papers have been published on BPPV, increasing imbalance with age and increasing falls, none has ever described the loss of otoconia as a major reason for this imbalance. Maybe this is due to the problems to proof this hypothesis in an individual patient.

We will explain why otoconial loss may cause dizziness, postural and locomotor instability in patients with no other identifiable cause or in addition to other causes. Several reasons can cause otoconial loss and lead to the described symptoms. We will describe the symptoms and the tests which could in combination support the diagnosis.

Conclusion: Our hypothesis argues for the new diagnosis in many patients with so far undiagnosed or incorrectly or incompletely diagnosed dizziness or imbalance.

Introduction/background

Otoconial loss and BPPV

Loss of otoconia from the utricle often leads to BPPV. We know, that the prevalence of BPPV increases continuously from a 1-year prevalence of 0.5% in the 18–39 year age group up to 3.4% in those aged 60 and older, reaching a cumulative lifetime incidence of 10% by the age of 80 [1].

The most common form of vertigo is idiopathic BPPV

BPPV can also be caused by head trauma [2]. Patients often experience lightheadedness, dizziness, or short-lasting unsteadiness following successful repositioning maneuvers for BPPV, which is called residual dizziness (RD) [3]. RD occurs with an incidence of 31–61% and more often with increasing age above 65 years [4]. Several reasons for RD are debated, such as anxiety or loss of utricular function. The latter

means, in general, a loss of utricular haircell function, rather than isolated otoconial degeneration, although von Brevern et al [5] suggested macular degeneration as consequence of a utricular lesion. One possible, so far overlooked, reason for RD may be isolated otoconial loss in the absence of haircell loss or damage, particularly for long lasting RD. The duration of RD is often estimated in weeks, but much longer imbalance is also reported [6,7]. The short lasting RD directly after successful repositioning maneuvers could also be explained by otoconia falling back on the utricle thus changing the sensation of gravity, i.e. our sensation of gravity could change with the changing weight of the otoconial membrane. Whether increasing or decreasing macular weights have different effects is still unknown.

Other causes of imbalance

Causes of postural and locomotor instability or dizziness other than RD are commonly thought to be nonspecific and multi-factorial; among

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these are cerebrovascular diseases, cervical spondylosis, whiplash injury, depressive state, poor vision, orthostatic hypotension, or low cerebrospinal fluid syndrome. They all may play a role in the development of dizziness [8]. Loss of haircells was found significantly less (about 25%) in the macula organs compared to the semicircular canal cristae (about 40%) [9]. One important factor which seems to have been missed so far is otoconial loss. Its consequences, other than BPPV, have not yet been considered in humans. However, animal studies show that missing otoconia with intact haircells cause lifelong balance problems [10,11]. In humans, only haircell-loss is generally considered a pathogenic factor for imbalance, despite the suggestion of Jones et al. [12] that gravity receptor neural function in lethal milk (lm) mouse mutants might be correlated with the severity of otoconial loss. These lm mutants lack utricular otoconia and have variable loss of otoconia in the saccule [13].

Assumed congenital lack of otoconia in a human has also been described in an oral presentation [14], imaging and a genetic mutation support the hypothesis and a manuscript is in preparation.

Loss of balance after head trauma or whiplash injuries is often explained by neck problems, which do occur quite often and thus seem to be correlated. Mallinson and Longridge [15] believed that abnormalities in computerized dynamic posturography are the result of disruption of tonic neck input into the linear vestibulo-ocular reflexes and are not caused by vestibular system damage. So, loss of otoconia was not suspected. A case of otoconial loss shown by bilateral BPPV and constant imbalance even after successful repositioning maneuvers has also been presented orally [16] a manuscript was recently rejected but will soon be submitted elsewhere.

According to Rieke [17], about 10% of patients involved in rear-end motor vehicle collisions suffer from whiplash, 18% to 40% have chronic pain in the upper cervical spine region, and 25% to 50% complain of vertigo and dizziness. This suggests there could be 10 to 32% with vertigo or dizziness but without neck pain.

But what is with the patients who resolve their neck problems and stay dizzy? Loss of otoconia is a possible explanation for such otherwise unexplained dizziness.

Otoconial degeneration increases above the age of 50 or 60 [18,19]. This degeneration was used to explain increasing prevalence of BPPV with age [1], but not yet the also increasing imbalance. In mammals, otoconia achieve full size within weeks of birth, and there is little evidence for further development [20]. Igarashi et al [21] found a decrease in otoconial volume of 41% in the utricle and 70% in the saccule comparing infants to older adults (58–87 years). To date, we couldn't find a paper correlating between otoconial loss and balance problems in the elderly separated from a loss of haircells, which also occurs but most likely much less than otoconial loss. At least Walther and Westhofen [22] have mentioned the combined loss of otoconia and haircells with age but didn't discern between both.

Increasing imbalance with age is a very common symptom. According to Baloh et al. [23] there is only a weak correlation of vestibular, visual, auditory, somatosensory dysfunction as well as white matter lesions with age related changes in gait and balance. Unfortunately, in their study only functions of the angular vestibuloocular reflex (VOR) were tested. Knowing that cVEMP and oVEMP are often absent with increasing age [24], a similar longitudinal study using macula function tests is warranted. We suggest otoconial loss to be the major reason for decreasing imbalance with age. The slowly progressive loss correlates well with a slowly increasing imbalance, which is very common in the elderly.

Otolith afferents are classified as regular or irregular firing. Irregular afferents have phase-tonic response dynamics [25], whereas regular afferents have tonic responses [26]. The irregular afferents are sensitive to acceleration and jerk (the derivative of acceleration), whereas regular afferents give sustained responses to static stimulation, so these have been termed 'transient' and 'sustained' pathways [27]. Notably, VEMPs selectively stimulate the transient system, whereas

tests with lower frequency stimulation such as the static tilt, which presumably selectively activate the sustained pathway, should be abnormal with otoconial loss. Thus, a patient with isolated otoconial loss could appear to have highly selective damage to the sustained pathway.

How can otoconial loss be tested?

Saccular function can only be measured with cervical vestibular evoked myogenic potentials (cVEMP) [28]. Theoretically, vertical translational VOR is also a possible measurement [29] but it is rarely performed in humans. Function of the transient utricular pathway can be measured by ocular vestibular evoked myogenic potentials (oVEMP) [30] and the sustained pathway by testing the subjective visual vertical or horizontal (SVV or SVH) in straight head position as well as in head- or whole-body-roll-tilt-positions or during eccentric rotation. Also fundus-photography is used to measure binocular cyclotorsion, which also belongs to the sustained pathway. Horizontal linear translation is also rarely done in patients, but a theoretical option.

C- and oVEMP deliver short air or bone conducted sound stimuli and the reflexes have very short latencies of about 10 and 13 ms (P10 and N13). It has been suggested that fluid pressure waves created by high frequency sound and vibration in VEMP tests directly stimulate hair cells connected to irregular striola afferents [31], and so may not depend on the otoconia movement to generate a response. On the other hand, Iversen et al. recently showed that low intensity ultrasound activated vestibular orolith organs in oyster toadfish through acoustic radiation force directly moving the otolith and that activation of irregular and regular haircells was decreased by about 90% without an otolith [32]. Nevertheless, they also mentioned in their paper, that cochlear haircells have not been activated by their stimulus so it is not yet proven that macula receptor haircells cannot be directly activated by loud noise without otoconia. Thus, while VEMP assess if the haircells and neural transient pathways are functional, they may not determine if the transduction of linear acceleration is normal. If they are reduced by loss of otoconia like suggested by Iversen et al. [32] this could also explain the progressively decreasing and often bilaterally missing c- and oVEMP amplitudes with age. In summary, it is not yet completely known, whether c- and oVEMP measure only the transient pathway while SVV/SVH measure the sustained pathway or whether both pathways can be involved. At least we are confident that tVOR needs otoconia for natural stimulation of haircells.

Otoconial loss with loss of haircells seems very likely, because inflammation or reduced blood supply to the macula organs can induce both. Therefore, abnormal oVEMP in about 56.7% of patients with BPPV have recently been described compared to 3.34% in controls without BPPV [33]. In other words, 43.3% of these BPPV patients had normal oVEMP i.e. may only suffer from otoconial loss. Whether otoconial loss alone causes a reduction of oVEMP and how many otoconia must be lost for abnormal oVEMP has yet to be determined.

Hypothesis

From the above mentioned knowledge and the two patients published so far by oral presentations [14,16], the following hypothesis is suggested:

Otoconial loss may be an ignored or underestimated reason for long lasting dizziness or imbalance after head trauma, increasing unsteadiness with aging as well as for RD after successful canalith repositioning maneuvers in BPPV and also for some forms of congenital imbalance. Tests of saccular and utricular function may give contrasting results like described in the following: c- and oVEMP responses maybe normal as testing the transient pathway, but SVV or SVH may be pathologic. SVV or SVH are possibly only pathologic during head- or whole-body-tilt and during eccentric rotation. Translational VOR may also reveal pathological results. Therefore, these tests in comparison with c- and oVEMP-results could support or deny the suspected diagnosis.

Thus, a patient with isolated otoconial loss would appear to have highly selective damage to the sustained pathway (SVV/SVH) and tVOR but probably normal cVEMP or oVEMP, depending whether otoconial loss occurred at both or only one of the macula-receptors.

We think it is unlikely that head trauma could be so selective as to just damage regular afferents, i.e. sparing striolar type I haircells and irregular afferents. Interestingly, it has been suggested that fluid pressure waves created by high frequency sound and vibration in VEMP tests directly stimulate irregular striolar hair cells [34]. This hypothesis is also supported by galvanic vestibular stimulation, which bypass the macula mechanics, have a latency only slightly shorter than VEMP [35]. Intact otoconia may then not be necessary for normal VEMP responses. We suggest that otoconial loss impairs sustained responses that depend upon the tight coupling of type II hair cells to the gelatinous layer and otoconia.

Acute unilateral lesions of saccular and utricular haircells e.g. during peripheral vestibulopathy are generally compensated quickly but we hypothesise that otoconial loss could cause a clinically persistent unsteadiness without any signs of neurologic, psychiatric or cervicogenic causes and without any lesion detectable in cerebral MRI. This could be seen in increased imbalance in darkness and pathological SVV in tilted body or head positions and during eccentric rotation.

Otoconia are thought to especially increase our sensation for gravity, i.e. linear acceleration. This is supported by the knowledge that knockout mice and guinea pigs without otoconia have lifelong balance problems and especially cannot swim [10,11]. Also in humans a congenital absence or lack of otoconia may exist as has also been shown in histological findings in two infants without otoconia [36,37] although symptoms couldn't been known and vestibular testing couldn't be performed in both babies. The first suspected congenital otoconial loss in an adult human has so far only been published orally [14]. Counting otoconia in living humans is not yet possible and it is unknown how many otoconia can be lost without developing symptoms others than BPPV. Thus, it is difficult to speculate as to how much otoconial loss needs to occur to cause a change of our sensation of gravity.

Since otoconial volume is reduced with age in the sacculle (70%) more than in the utricule (40%) [18] this could induce lower gains for vertical tVOR, like described in one oral presentation [16]. With two patients showing the behavior fitting to our hypothesis and their vestibular testings also nicely supporting our hypothesis of a congenital or traumatic loss of otoconia, we can only speculate that there are many more patients suffering from otoconial loss. But with known otoconial degeneration with aging and many patients with "unexplained" dizziness after head trauma and whiplash injuries, we think that the presented hypothesis is logical and explained well. We hope that many cases according to our hypothesis will be published soon.

Because of otoconia progressively degenerating with age [18,19] we suspect a possible connection between degenerating otoconia and the slowly increasing imbalance with age. Of course there are multifactorial reasons for decreasing imbalance with age like decreasing vision, hearing, sensibility (polyneuropathy), muscle strength as well as increasing cervicogenic problems, but we propose that loss of otoconia is one additional and important factor. This factor is up to now being forgotten or ignored.

We want to keep in mind that c- and oVEMP are not the only macula tests available and that SVV with the head upright, in different tilt positions and during eccentric rotation are also important tests. We recommend to perform these tests for the sustained pathway in addition to c- and oVEMP and, if possible, also tVOR. Unfortunately, there is yet no test available to objectively prove this new diagnosis.

Conclusion

In conclusion we suggest to think of otoconial loss as a separate factor beside haircell function. It's effect on gait and balance has been orally described in the example of two patients, one with a congenital

lack of otoconia and the other with a traumatic loss of otoconia. We suspect that many patients with similar symptoms also suffer from otoconial loss or lack of otoconia. We suggest the following classification of symptoms for which otoconial loss should be included in the differential diagnosis or as a partial component of the symptoms:

- Traumatic otoconial loss
 - o Persistent dizziness or postural and locomotor instability after
 - whiplash injury,
 - head trauma
 - traumatic brain injury (TBI)
- Degenerative otoconial loss
 - o Imbalance with aging
 - o Residual dizziness after BPPV
 - o postural and locomotor instability with no other identifiable cause
- Congenital lack of otoconia

We hope that this new diagnosis will lead to major scientific investigations on the metabolism and possible medical support for otoconial regeneration.

Declaration of Competing Interest

I have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.05.002>.

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