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Otolithic Membrane Damage in Patients with Endolymphatic Hydrops and Drop Attacks

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Abstract

Objectives—1. Evaluate the otolithic membrane in patients with endolymphatic hydrops (EH) and vestibular drop attacks (VDA) undergoing ablative labyrinthectomy. 2. Correlate intraoperative findings to archival temporal bone specimens of patients with EH.

Study Design—Retrospective case review

Setting—Tertiary referral center

Specimen source—1. Patients undergoing labyrinthectomy for incapacitating Meniere's disease (MD), delayed EH, VDA, or acoustic neuroma (AN) between 2004 and 2011. 2. Archival temporal bone specimens of patients with MD.

Interventions—Ablative labyrinthectomy

Main outcome measures—Examination of the utricular otolithic membrane.

Results—The otolithic membrane of the utricle was evaluated intraoperatively in 28 patients undergoing labyrinthectomy. 7 (25%) had a history of VDA, 6 (21%) had delayed EH, 9 (32%) had MD, and 6 (21%) had AN. All patients with VDA showed evidence of a disrupted utricular otolithic membrane, whereas only 50% and 56% of patients with delayed EH and MD respectively, demonstrated otolithic membrane disruption ($p = 0.051$). None of the patients with AN showed otolithic membrane disruption ($p = 0.004$). The mean thickness of the otolithic membrane in 5 archival temporal bone MD specimens was 11.45 micrometers versus 38 micrometers in normal specimens ($p=0.001$).

Conclusions—The otolithic membrane is consistently damaged in patients with VDA. In addition, there is a significantly higher incidence of otolithic membrane injury in patients with MD and delayed EH compared to patients without hydrops, suggesting that the underlying

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pathophysiology in VDA results from injury to the otolithic membrane of the saccule and utricle, resulting in free-floating otoliths and atrophy.

Introduction

Vestibular drop attacks (VDA) are sudden violent falls, which are present in a small subset of patients with endolymphatic hydrops (EH) (1–4). VDA, also known as Tumarkin falls, were first described by Tumarkin in 1936. These are sudden falls without loss of consciousness and without any neurologic symptoms or sequelae that occur in patients with Meniere's disease (MD) (1). Patients describe being pushed down to the ground with tilting of the surrounding environment, and they tend to have multiple falls in the same direction (4).

VDA typically occur in patients with late or end-stage EH (2). EH refers to distention of the endolymphatic structures within the inner ear found on histopathology, and is most commonly associated with MD (5). MD clinically manifests as fluctuating hearing loss, tinnitus, and episodic vertigo. Delayed endolymphatic hydrops (DEH) shares a common histopathology with MD, but is a clinical entity distinct from MD. DEH presents as episodic vertigo in patients who have longstanding unilateral profound sensorineural hearing loss (SNHL), most commonly from early childhood (6). The underlying pathophysiology in both MD and DEH remains elusive, though they share the same histopathologic finding of endolymphatic hydrops.

VDA are present in 3–7% of patients in both MD and DEH (3, 7). VDA have also been rarely reported in patients without MD or DEH, possibly associated with migraine (8–9). While some case series suggest spontaneous remission of VDA (3, 10–11), most authors now agree that successful treatment can only be achieved through ablation of the peripheral vestibular system, via intratympanic gentamicin, vestibular nerve section, or transmastoid labyrinthectomy (2, 4, 12).

Based on its clinical features, the most widely accepted mechanism of VDA is a sudden stimulation of the otolith organs. VDA are therefore also known as “otolithic crises”. Mechanical stimulation of the otoliths in the utricle and/or saccule could activate vestibulospinal pathways, triggering a fall (1, 8).

The cause of otolith stimulation remains unknown, although there is speculation that pressure gradients within the inner ear could result in mechanical deformation of the otolithic membrane of the utricle or saccule, precipitating attacks (3). Recent studies have shown abnormalities in the vestibular evoked myogenic potentials (VEMP) in patients with VDA, lending support to the hypothesis that VDA arise from otolith organ dysfunction (13–14).

There has been no study to our knowledge examining the otolithic membrane in patients with VDA. We hypothesized that VDA result from injury to the otolithic membrane of the saccule and utricle, resulting in a disrupted otolithic membrane characterized by free-floating otoliths. We tested this hypothesis by examining the otolithic membranes in patients with MD, DEH, VDA, and acoustic neuromas (AN) undergoing transmastoid

labyrinthectomy. In addition, we compared the utricular otolithic membrane from archival temporal bone specimens between patients with and without MD.

Materials and Methods

Archival temporal bone specimens

The Institutional Review Board (IRB) of UCLA has approved this study. Appropriate informed consent for inclusion in the study was obtained from each temporal bone donor before death as part of a National Institute of Health (NIH) funded Human Temporal Bone Consortium for Research Resource Enhancement through the National Institute on Deafness and Other Communication Disorders (NIDCD). The vestibular endorgans were microdissected from each donor. Human temporal bone specimens were obtained post-mortem from five subjects with a history documenting a lack of auditory or vestibular symptoms and from five subjects with documented MD.

The thickness of the otolithic membrane in each utricle was evaluated using the Microsuite™ Five (MS5) software run on a Dell Precision 380 computer, coupled to the light microscope Olympus BX51. Images were captured using a CCD camera DP70 attached to the microscope. Statistical analysis of the data obtained was performed on SAS software using a 2-sample t-test.

Vestibular endorgans obtained from surgery

The otolithic membrane of the utricle was examined intraoperatively in a total of 28 patients undergoing transmastoid labyrinthectomy. 22 patients had DEH/MD with or without VDA. All patients had intractable vertigo spells and/or VDA despite medical management and had non-functional hearing in the operated ear (defined as word discrimination score less than 20%). All patients with MD met the 1995 AAO-HNS criteria for definitive Meniere's disease (Committee on Hearing and Equilibrium 1995). 6 patients underwent transmastoid labyrinthectomy for excision of an AN.

The otolithic membranes of the utricle were evaluated using the Zeiss 8 intraoperative microscope with photo-documentation using the Tricam Image 1 Camera and the Stryker Aida image capture system. Intraoperative photographs, clinical histories, audiograms, and vestibular testing data were collected and analyzed retrospectively. Statistical analysis between groups of patients was performed using Fisher's Exact Test.

Results

Disrupted otolithic membranes in patients with VDA

7 patients (ages ranging from 33 to 83 years) underwent ablative labyrinthectomy for intractable VDA. Of these seven patients, 5 had a history of MD and 2 had a history of DEH. All patients had preoperative profound sensorineural hearing loss and decreased caloric responses on the operated side.

In the 5 patients with a history of MD, the age range was 47 to 81 years. All 5 patients had symptoms of MD for several years prior to developing VDA. 2 of these patients also had a history of migraine headaches.

Of the two patients with a history of DEH, one was a 66-year old male with a 17-year history of profound hearing loss prior to developing episodic vertigo. He then developed several episodes where he described the world turning upside down while driving and was subsequently diagnosed with VDA. The other patient with a history of DEH was a 33-year-old female with deafness since childhood after contracting mumps, who developed severe episodic vertigo more than 25 years later with several episodes of violent dizziness, which she described as throwing her to the floor from a sitting position.

During ablative labyrinthectomy, aggregates of otoconia were observed to be free-floating on the surface of the utricular membrane in 6 of 7 patients who had a history of VDA with evidence of membrane disruption (Fig. 1A–B, Table 1). The remaining patient had severe atrophy of the utricular membrane without an identifiable otolithic membrane (Fig. 1C). The spectrum of otolithic membrane disruption is shown in Figure 1 through intraoperative photographs of three representative patients. All patients underwent successful vestibular rehabilitation therapy and were discharged home between postoperative days 2 and 4. Ablative surgery was curative of the VDA and vertigo spells in all cases.

Otolithic membrane disruption in patients with MD and DEH

The utricular membrane was also evaluated intraoperatively in 15 patients undergoing ablative labyrinthectomy for intractable vertigo due to DEH and MD without VDA. 6 of these patients (ages ranging from 23 to 76 years) had a history of DEH, and 9 had a history of MD (ages ranging from 45 to 60 years). All patients had severe to profound SNHL and vestibular paresis on the operated side prior to ablative labyrinthectomy.

Of the 9 patients with MD, 5 patients (56%) had a disrupted otolithic membrane intraoperatively with either floating or absent aggregates of otoconia (Fig. 2B). The other 4 patients had normal appearing otolithic membranes (Fig. 2A). In the 6 patients with DEH, 3 patients (50%) had intraoperative findings of floating otoconia debris along the utricular membrane (Fig. 2D). The other 3 patients had a normal appearing utricular membrane (Fig. 2C).

There was a trend toward the presence of a disrupted otolithic membrane and floating otoconia in patients with MD/DEH with VDA versus those without VDA ($p=0.051$, Table 1).

Normal otolithic membrane in patients undergoing AN excision

6 patients (age ranging from 35 to 63 years) underwent a translabyrinthine approach for excision of an AN. In all 6 patients, the otolithic membrane of the utricle was intact without floating otoconia or debris (Fig. 3). The absence of damage to the utricular membrane was significant when compared to the group of patients with MD/DEH without VDA as well as to the group of patients with VDA ($p<0.05$, Table 1). In addition, the proportion of floating otoconia and otolithic membrane damage significantly differed when compared between all

3 groups of patients: VDA, MD/DEH without VDA, and AN ($p=0.002$). There was no statistically significant difference in otolithic membrane damage across groups between patients older than 60 years versus younger patients.

Decreased thickness of the otolithic membrane in archival MD temporal bone specimens

The utricular otolithic membrane thickness was evaluated in 5 temporal bone specimens from patients with documented normal audiovestibular function, and in 5 specimens from patients with documented MD. The mean thickness of the otolithic membrane in the 5 archival temporal bone MD specimens was 11.45 micrometers versus 38 micrometers in normal specimens ($p=0.001$, Fig. 4).

Discussion

Endolymphatic hydrops resulting in incapacitating episodic vertigo is a devastating illness, which renders patients unable to perform their daily activities of living. VDA are even more disabling, as patients have no warning prior to being thrown involuntarily to the ground in oftentimes violent falls (15). VDA occur in only a small subset of patients with MD and DEH, and the recommended treatment option is ablation of the peripheral vestibular system due to the dangerous nature of the falls.

While the clinical entity of VDA has been thoroughly described, the underlying pathophysiology remains elusive. In the present study, we describe the finding of disrupted otolithic organ membranes and floating aggregates of otoliths in a series of patients with VDA undergoing ablative labyrinthectomy. We also show a difference in the proportion of patients with otolithic membrane injury when comparing patients with EH and VDA compared to those without EH or VDA.

The widely believed theory that VDA arise from the utricle and/or saccule (i.e., the otolithic organs) is generated from two findings: VDA are eliminated by surgical ablation of the vestibule and clinical symptoms are consistent with sudden mechanical stimulation of the otolithic organs (13). Recent data examining VEMPs, a test based on acoustic stimulation of the saccule, in patients with VDA suggests that otolithic organ damage is involved in the underlying pathophysiology of VDA. Timmer et al. showed a higher proportion of altered VEMP responses in MD patients with VDA than in those without VDA. VEMP thresholds were more commonly absent in patients with VDA. They also found altered tuning and a gradient of elevated thresholds that corresponded to disease severity in EH with and without VDA (13). Unstable otolithic function was also suggested by Ozeki et al., who showed reversible changes in VEMP responses after glycerol administration in patients with MD and VDA (14).

We believe otolithic organ dysfunction is a continuum in the disease process of MD. VEMPs have been previously shown to be depressed or absent and to correlate with the stage of MD (16). Our data also supports the notion that otolithic membrane injury is present to some degree in patients with MD or DEH without VDA when compared to the group of patients without EH undergoing AN excision (Table 1).

Although our data supports the notion that otolithic organ injury is likely a continuum in the process of EH (encompassing MD, DEH, and VDA), it remains unclear why only certain patients with EH develop VDA. Aside from VEMP testing, there are not any significant differences in quantitative auditory and vestibular function between MD patients with and without VDA (17). Moreover, a recent temporal bone study by Merchant et al. concluded that EH is merely a histologic marker of MD (5). EH is likely a necessary, but insufficient condition for the development of MD, as there are temporal bones with EH from subjects without symptoms of MD.

The otolithic organs appear to be an important factor in the underlying disease process of MD/delayed EH, and in VDA associated with EH. In the present study, the archival temporal bones demonstrate degeneration of the utricular membrane in MD specimens when compared to normal specimens, with significantly decreased thickness of the otolithic membrane (Fig. 4). This data suggests that damage to the otolithic organs occurs as part of the underlying pathophysiology of MD. There are no other studies to our knowledge specifically examining the otolithic membranes in patients with MD.

Otolithic organ dysfunction and MD is also suggested by the subset of MD patients that develop benign paroxysmal positional vertigo (BPPV), known as secondary BPPV. These patients develop BPPV on the same side as the MD, which argues against two simultaneous coincidental pathologies (18–19). One theory is that loose otoconia from BPPV causes decreased endolymphatic absorption, resulting in EH (20). The other proposed explanation is that EH in MD causes damage to the otolithic membrane of the utricle, resulting in loose otoconia and the subsequent clinical entity of BPPV (21). This theory is supported by the fact that the majority of patients with MD and BPPV report MD symptoms preceding BPPV symptoms (18, 21).

Interestingly, we have observed anecdotally the development of classic VDA 24–48 hours after performing the Epley maneuver for treatment of BPPV in four patients without any evidence of inner ear disease. As mentioned previously, VDA have been reported in patients without EH (8–9). These cases suggest that VDA may in fact result from intrinsic properties within the otolithic membrane itself.

There are multiple studies specifically isolating proteins necessary for the assembly and maintenance of the otoconia complex and sensory epithelium of the otolithic organs (22). Specifically, the inner ear protein otogelin (*otog*) has been shown in knockout mice to be required for anchoring of the otoconial membranes to the neuroepithelia; histologically, otoconial membranes were found to be detached from the neuroepithelia and either stuck to the roof of the structures or floating in endolymph in *otog*^{-/-} mice (23). Otoconin-90 (Oc90) is another protein recently isolated, which is specific to the vestibular otolithic membrane. Oc90 deletion in mice leads to the formation of giant otoconia and was shown to be necessary for the formation of the organic matrix of otoconia by recruiting other matrix components (24–25).

Further studies examining the molecular and protein makeup of the macular sensory epithelium of the otolithic organs in patients with EH and VDA will be important to shed light into the underlying pathophysiology of EH and VDA.

Conclusions

The otolithic membrane is consistently damaged in patients with VDA. In addition, there is a significantly higher incidence of otolithic membrane injury in patients with MD and delayed EH compared to patients without hydrops, suggesting that the underlying pathophysiology in VDA results from injury to the otolithic membrane of the saccule and utricle, resulting in free-floating aggregates of otoconia and atrophy of the otolithic membranes.

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Fig. 1. Disrupted otolithic membranes in patients with Vestibular Drop Attacks (VDA)

A, Right ear, utricular membrane (large arrow) partially disintegrated at edges with free-floating otoliths (short arrows). **A1**, High magnification view of **A**. **B**, Left ear, Otolithic membrane (large arrow) more grossly disintegrated with aggregates of floating otoconia (short arrows). **B1**, Higher magnification of **B**. **C**, Right ear, Atrophic utricular membrane with complete absence of otoconia and membranous tissue (arrow points to area of the utricle). **C1**, Higher magnification. Sup, superior; I, inferior; Ant, anterior; Post, posterior, * area of superior semicircular canal

Fig. 2. Otolithic membranes in patients with Meniere's Disease (MD) and Delayed Endolymphatic Hydrops (EH)

A, Normal appearing otolith membrane of the utricle in Meniere's Disease (MD) patient, Left Ear. The utricular membrane (arrow) is intact without free-floating otoliths. **A1**, Higher magnification. **B**, Disrupted otolith membrane of the utricle with floating groups of otoconia in MD patient, Left Ear. The utricular membrane (arrow) is irregular with free-floating aggregates of otoliths (short arrows). **B1**, Higher magnification. **C**, Normal otolith membrane in patient with delayed EH, Left Ear. The utricular membrane (arrow) is

intact without free-floating otoliths. 2C2, Higher magnification view. **D**, Disrupted otolithic membrane with floating otoconia in patient with delayed EH, Right Ear. The utricular membrane (arrow) is irregular with free-floating groups of otoliths . 2D1, Higher magnification view showing groups of floating otoconia (short arrows). Sup, superior; I, inferior; Ant, anterior; Post, posterior, * area of superior semicircular canal

Fig. 3. Normal otolithic membrane of the utricle in a patient undergoing Acoustic Neuroma (AN) excision, Left ear

A, The utricular membrane (arrow) is intact without free-floating otoliths. **B**, Higher magnification view. Sup, superior; I, inferior; Ant, anterior; Post, posterior, * area of superior semicircular canal

Fig. 4. Decreased thickness of the utricular otolithic membrane in archival temporal bone specimens of Meniere's Disease (MD) patients

Table 1

Otolithic membrane damage in vestibular drop attacks. The presence of otolithic organ damage significantly differed across all groups, $p=0.002$. N, number.

Diagnosis	N (total n =28)	N, Disrupted utricular membrane	p value
Vestibular drop attacks (VDA)	7 (25%)	7 (100%)	0.051
Delayed endolymphatic hydrops without VDA	6 (21%)	3 (50%)	
Meniere's disease without VDA	9 (32%)	5 (56%)	
Acoustic Neuroma	6 (21%)	0 (0%)	0.004