Pathologic Changes of the Peripheral Vestibular System Secondary to Chronic Otitis Media

Rafael da Costa Monsanto1,2, Mehmet Erdil1,3, Henrique F. Pauna1,4, Geeyoun Kwon, PhD1, Patricia A. Schachern1, Vladimir Tsuprun, PhD1, Michael M. Paparella1,5, and Sebahattin Cureoglu, MD1

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Abstract

Objective. To evaluate the histopathologic changes of dark, transitional, and hair cells of the vestibular system in human temporal bones from patients with chronic otitis media.

Study Design. Comparative human temporal bone study.

Setting. Otopathology laboratory.

Subjects and Methods. To compare the density of vestibular dark, transitional, and hair cells in temporal bones with and without chronic otitis media, we used differential interference contrast microscopy.

Results. In the chronic otitis media group (as compared with the age-matched control group), the density of type I and type II hair cells was significantly decreased in the lateral semicircular canal, saccule, and utricle (P < .05). The density of type I cells was also significantly decreased in the chronic otitis media group in the posterior semicircular canal (P = .005), but that of type II cells was not (P = .168). The mean number of dark cells was significantly decreased in the chronic otitis media group in the lateral semicircular canal (P = .014) and in the posterior semicircular canal (P = .002). We observed no statistically significant difference in the density of transitional cells between the 2 groups (P > .1).

Conclusion. The findings of our study suggest that the decrease in the number of vestibular sensory cells and dark cells could be the cause of the clinical symptoms of imbalance of some patients with chronic otitis media.

Keywords

chronic otitis media, dizziness, vertigo, vestibule, hair cells, dark cells, transitional cells, temporal bone, histopathology

Worldwide, otitis media is one of the most common infectious diseases and a significant cause of hearing impairment.1 According to the US Department of Health and Human Services, $2.8 billion was spent in 2006 alone to treat otitis media and its complications in children, not including over-the-counter medications.2 Clinically, chronic otitis media is defined as middle ear effusion and/or drainage for at least 3 months. Histopathologically, chronic otitis media is characterized by intractable changes of the middle ear and mastoid cavity, such as granulation tissue and cholesteatoma.3

Functional and structural damage of the cochlea secondary to chronic otitis media has been reported.4,5 Studies show that inflammatory mediators and bacterial products can spread through the round window membrane and into the labyrinth, damaging the organ of Corti, lateral wall, and other structures of the cochlea.4,6-9 Furthermore, patients with chronic otitis media frequently experience dizziness and/or vertigo; such symptoms suggest that the inflammation can also affect the vestibular system, given its anatomic proximity to the cochlea.4,5 Up to 53.5% of patients with chronic otitis media experience vertigo, which is associated with changes in the results of rotational chair, caloric, and vestibular evoked myogenic potential tests.10

To our knowledge, however, no study has been published on the histopathologic changes of vestibular cells in patients with chronic otitis media. In this study, our objective was to

1Department of Otolaryngology–Head and Neck Surgery, University of Minnesota, Minneapolis, Minnesota, USA
2Department of Otolaryngology and Head and Neck Surgery, Banco de Olhos de Sorocaba Hospital, Sorocaba, Brazil
3Department of Otolaryngology, Head and Neck Surgery, Bagcilar Training and Research Hospital, Istanbul, Turkey
4Department of Otolaryngology and Head and Neck Surgery, Bagcilar Training and Research Hospital, Istanbul, Turkey
5Department of Otolaryngology and Head and Neck Surgery, Campinas State University, Campinas, Brazil
6Paparella Ear Head and Neck Institute, Minneapolis, Minnesota, USA

Corresponding Author:
Sebahattin Cureoglu, MD, Otopathology Laboratory, Department of Otolaryngology, University of Minnesota, 2001 6th St SE, Lions Research Building, Room 210, Minneapolis, MN 55455, USA.
Email: cureo003@umn.edu
evaluate the histopathologic changes of dark, transitional, and hair cells of the vestibular system in human temporal bones from patients with chronic otitis media.

**Material and Methods**

**Samples**

The initial chronic otitis media group in our study included human temporal bones with intractable tissue changes in the middle ear, such as cholesteatoma, granulation tissue, fibrosis, tympanosclerosis, and cholesterol granuloma. Excluded from this group were temporal bones from patients who had tumors affecting the ear; who underwent either irradiation of the head and neck or chemotherapy; who had a history of aminoglycoside use (either topical or systemic); who underwent any otologic surgery other than tympanostomy tube insertion; who had Ménière’s disease, clinical otosclerosis, or a systemic autoimmune disease; or whose temporal bones were affected by processing artifacts. The final chronic otitis media group (Table 1) included 23 temporal bones from 19 men and 4 women; their mean age was 61.13 ± 18.37 years (range, 18-93 years).

The control group included 23 temporal bones from patients without any sign of ear disease who were age matched to the chronic otitis media group; their mean age was 58.60 ± 18.01 (range, 18-92 years).

The temporal bones that we used in our study had previously been harvested during autopsy, fixed in 10% buffered formalin, decalcified with ethylenediaminetetraacetic acid, dehydrated in graded concentrations of alcohol, and embedded in celloidin. Each temporal bone was serially sectioned in the horizontal plane at a thickness of 20 μm. Every 10th section was stained with hematoxylin and eosin, then mounted on a glass slide. Three of the authors were responsible for scrutinizing the temporal bones. The authors were blinded from some patient information, including sex, age, and medical history. The results found among the authors were compared to ensure interobserver agreement.

The Institutional Review Board of the University of Minnesota approved this study (0206M26181).

**Hair Cells**

To measure hair cell density, we scrutinized every 10th horizontal section of the following vestibular structures: (1) the maculae of the saccule and utricle and (2) the cupulae of the lateral and posterior semicircular canals (Figure 1). In many of the temporal bones, the anterior semicircular canal was absent, probably because of issues related to removal or processing; therefore, we did not analyze vestibular cells in this structure.

We distinguished cells by their morphologic characteristics: type I cells are pyriform, with a spherical nucleus, and are surrounded by a nerve chalice; in contrast, type II cells are shaped like a cylinder, with a cylindrical nucleus, and do not have a nerve chalice.

To measure vestibular hair cell density, we evaluated type I and II cells under a differential interference contrast microscope (AxioCam; Carl Zeiss Microscopy, Pleasanton, California) at 1250× magnification. We counted both hair cell types separately, within a width of 500 μm, using the criteria of Merchant. We counted only cells that had an identifiable nucleus (Figure 2). To avoid overestimation of data, we corrected the raw hair cell density using the formula of Abercrombie. The final cell density was expressed as the number of cells per surface area of 0.01 mm².

**Dark Cells**

To compare the number of dark cells between the 2 groups (the chronic otitis media group and the control group), we evaluated every 10th section, including the crista ampullaris of the lateral and posterior semicircular canals, under light microscopy. We distinguished dark cells from the surrounding supporting cells by their characteristics: (1) intimate contact with melanin granules and (2) nuclei positioned high and close to the endolympathic space (Figures 1 and 3). We counted every dark cell within 100 μm of the transitional epithelium that had an identifiable nucleus, as previously described. The results were expressed as the number of dark cells per area within 100 μm of the transitional epithelium.

**Transitional Cells**

To compare the number of transitional cells between the 2 groups, we evaluated every section, including the crista ampullaris of the lateral and posterior semicircular canals, under light microscopy. We counted transitional cells in the same side of the cupulae that we used to count dark cells. We defined transitional cells as the cells between the ciliated epithelium and the dark cells (Figures 1 and 3). The results were expressed as the number of transitional cells per area in the vestibular compartment.

**Statistical Analysis**

To calculate and compare the density of hair, dark, and transitional cells in the 2 groups, we used the nonparametric Mann-Whitney U test (SPSS 22.0 for Windows; SPSS Inc, Chicago, Illinois). All results were expressed as the mean ± SD. Findings were considered statistically significant when \( P < .05 \).

**Results**

Of the 23 temporal bones in the chronic otitis media group, 19 (82.60%) had signs of effusion in the middle ear: mucoid effusion in 6 (31.57%), serous effusion in 6 (31.57%), and purulent effusion in 7 (36.86%). In addition, of the 23 temporal bones in the chronic otitis media group, 11 (47.82%) had signs of active infection, defined as the presence of inflammatory cells in the middle ear cleft.

**Hair Cells**

In the chronic otitis media group (as compared with the control group), the density of type I hair cells was significantly decreased in the lateral semicircular canal (\( P = .022 \),
posterior semicircular canal ($P = .005$), saccule ($P = .037$), and utricle ($P = .0003$). The density of type II hair cells was also significantly decreased in the chronic otitis media group in the saccule ($P = .038$), utricle ($P = .034$), and lateral semicircular canal ($P = .019$) but not in the posterior semicircular canal ($P = .168$; Figure 4).

For 11 of the 23 temporal bones in the chronic otitis media group, the charts included information about dizziness and/or imbalance. No information of the presence or absence of the symptoms was found in the charts of the other 12 patients; thus, they were not included in the following analysis. Among those 11 temporal bones, 5 did not experience those symptoms, while the other 6 included descriptions of a balance disorder. The density of both types of hair cells was higher in all vestibular system in the subgroup of 6 patients without dizziness and/or imbalance when compared with the subgroup with those complaints, except for the number of type II hair cells in the lateral and posterior semicircular canal ampullae. Nonetheless, the difference was not statistically significant ($P > .1$; Figure 4).

Within the chronic otitis media group, we also compared hair cell density in the subgroups with versus without signs of active infection. The difference between these 2 subgroups was also not statistically significant ($P > .2$; Figure 4).
Dark Cells

The mean number of dark cells in the lateral semicircular canal was 14.15 ± 1.97 in the chronic otitis media group and 15.87 ± 2.11 in the control group (P = .014). The mean number of dark cells in the posterior semicircular canal was 14.27 ± 2.98 in the chronic otitis media group and 16.66 ± 1.81 in the control group (P = .002). Thus, the mean number of dark cells was significantly decreased in the chronic otitis media group in both structures (Table 2).

Transitional Cells

The mean number of transitional cells in the lateral semicircular canal was 18.16 ± 4.13 in the chronic otitis media group and 19.20 ± 4.12 in the control group (P = .372). The mean number of transitional cells in the posterior semicircular canal was 17.875 ± 5.45 in the chronic otitis media group and 18.44 ± 2.06 in the control group (P = .135). We observed no statistically significant difference in the density of transitional cells between the 2 groups (P > .1).

Discussion

Many studies have demonstrated a relationship between chronic otitis media and functional and structural damage of the inner ear. Inflammatory mediators and toxins can pass into the inner ear through the round window membrane and cause loss of cochlear inner and outer hair cells. Such changes have clearly been associated with the high-frequency sensorineural hearing loss observed in patients with chronic otitis media. In a previous analysis of human temporal bones from patients with chronic otitis media, we observed a significant loss of outer and inner hair cells and a significantly decreased area of stria vascularis and spiral ligament in the basal cochlear turn, consistent with high-frequency sensorineural hearing loss. In a mouse experimental model, investigators reported inflammatory gene expression and gene products in the inner ear after acute otitis media. Those gene products were proven to affect inner ear ion and water transport functions, suggesting a possible mechanism for the permanent hearing loss seen in some patients with chronic otitis media.

That same mechanism appears to affect the vestibular system, given its anatomic proximity. Using vestibular diagnostic testing, Lee et al found that 25% of patients with chronic otitis media had abnormal caloric results in the affected side. Another study reported that 76% of patients with chronic otitis media had abnormal caloric results; in addition, 72% had abnormal results in the rotational chair. Using vestibular evoked myogenic potential tests, Wang et al noted that response rates were significantly delayed, both preoperatively and postoperatively, despite a significant improvement in the air-bone gap at 500 Hz after mastoid surgery; those findings point to damage of type I and II vestibular hair cells by inflammatory mediators secondary to chronic otitis media.

In another study of temporal bones from patients with chronic otitis media, the results of videonystagmography,
otoscopy, audiometry, ocular and cervical vestibular evoked myogenic potential tests, and imaging demonstrated that inner ear deficits can be detected early in the saccule and utricle, spreading to the cochlea and semicircular canals over time. Those findings support the hypothesis that the middle ear inflammatory components can also affect the vestibular organs and that the vestibular compartments closer to the round window are damaged first.

Several clinical studies demonstrated that otitis media can be the cause of balance issues. Aarhus et al, in a cohort study including 21,962 patients, observed that children with chronic suppurative otitis media and hearing loss after recurrent episodes of otitis media have a higher risk of dizziness in adulthood when compared with children with no history of ear diseases. Studies including posturography evaluation demonstrated that children with otitis media have a higher velocity of sway and increased difficulty performing the test when compared with the normal controls. These results provide clinical evidence of the damage on the peripheral vestibular system secondary to otitis media, stressing the importance of the early treatment and prevention of the different types of otitis media.

The vestibular hair cells are responsible for transducing minute displacement of endolymph into behaviorally relevant receptor potentials in a mechanotransduction system, providing the basis for vestibular function. The dark cells have been reported as being morphologically similar to the cochlear marginal cells, underscoring their role in endolymph production in the inner ear and fluid transport. Despite the morphologic similarities, the cochlear cells maintain an endocochlear potential of +80 mV, while the endovestibular potential in the semicircular canals is about +1 mV.

With regard to transitional cells, recent studies supported their role in ion transportation and in formation of the endolymphatic fluid.

Our study supports the hypothesis that histopathologic changes due to chronic otitis media occur in the vestibular system of the inner ear and appear to be similar to changes that we previously reported in the auditory system. Specifically, the loss of vestibular hair cells and dark cells seems to be responsible for the clinical symptoms of dizziness and/or imbalance; it also explains the abnormal results of functional tests in patients with chronic otitis media.

**Conclusion**

In this study, we found that human temporal bones from patients with (vs without) chronic otitis media showed a significant loss of type I hair cells, type II hair cells, and dark cells—but not loss of transitional cells—in different compartments of the vestibular system. The decrease in the sensory cells in the vestibule seems to be responsible for the clinical symptoms of dizziness and/or imbalance in patients with chronic otitis media.

**Author Contributions**

Rafael da Costa Monsanto, substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Mehmet Erdil, substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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**Disclosures**

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