The Laryngoscope

Comparative Histopathologic Analysis of Inner Ear Damage in Meningitis: Otogenic Versus Meningogenic Routes

Artur K. Schuster, MD; Nevra K. Yilmaz, DVM, PhD; Tomotaka Shimura, MD; Sebahattin Cureoglu, MD; Rafael da Costa Monsanto, MD, PhD; Joel Lavinsky, MD, PhD

Objective: To distinguish the patterns of inner ear changes between meningogenic and otogenic routes in meningitis cases. Our hypothesis is that pinpointing distinct patterns linked to each route could aid in the development of diagnostic strategies and targeted therapies.

Methods: Temporal bones (TBs) from patients with a history of meningitis and histopathological evidence of labyrinthitis were divided into two groups (otogenic and meningogenic). Inner ear histopathological examination was performed to identify qualitative and semi-quantitative changes. This assessment encompassed inflammation patterns, indications of early ossification, hair cell loss, and alterations in the lateral wall, round window membrane, cochlear aqueduct and vestibular aqueduct.

Results: Thirty-six TBs were included in the study (otogenic, 21; meningogenic, 15). Generalized labyrinthitis was more common in otogenic cases (100% vs. 53%, $p < 0.001$). Early signs of cochlear ossification were exclusively observed in otogenic cases (9 TBs). The spiral ligament of otogenic cases has shown a uniform loss of fibrocytes across all cochlear turns, while meningogenic cases showed more severe loss in the apical turn. Otogenic cases exhibited a higher prevalence of severe inflammation of the cochlear aqueduct and endolymphatic sac. Meningogenic cases showed more severe loss of vestibular hair cells in the otolithic organs.

Conclusion: Otogenic cases displayed a higher prevalence of changes in the spiral ligament and signs of early ossification, whereas meningogenic cases were associated with a higher degree of vestibular damage. Our findings emphasize the importance of considering the infection route and its implications for timely diagnosis and development of pathology-oriented treatment strategies.

Key Words: human temporal bone, labyrinthitis, meningitis, otopathology.

Level of Evidence: NA

***Laryngoscope*, 135:864–872, 2025**

INTRODUCTION

Meningitis poses a significant global health challenge, characterized by substantial morbidity and mortality rates.[1,2] The incidence of meningitis ranges from 0.5 to 207.4 per 100,000 individuals worldwide.[2] In 2016, a total of 2.82 million incident cases were reported globally.[2] Sensorineural hearing loss is a prevalent complication, affecting up to 54% of patients.[3–5]

Otitis media (OM), a widespread infectious disease, can progress to bacterial meningitis. In fact, meningitis emerges as the most frequent (12%–72%) intracranial complication of OM.[6] Limited research has explored the prevalence of otogenic infection among meningitis cases. A recent study (2024) has identified OM as the cause of meningitis in 31% of all cases.[7]

In cases of meningitis, the inner ear can be affected through two distinct routes. In otogenic labyrinthitis, the inner ear serves as a "conduit" for the middle ear infection to reach the meninges. In meningogenic labyrinthitis, the inner ear is affected retrogradely, either by direct spread through the inner ear aqueducts or the modiolus, or by hematogenous spread through the stria vascularis (SV).[8–10] Irrespective of the route of infection, labyrinthine infection can lead to a spectrum of progressive inflammatory changes including labyrinthitis ossificans. Up to 70% of patients with meningitis who develop profound sensorineural hearing loss have significant cochlear ossification.[11] Cochlear ossification poses a critical surgical challenge for cochlear implantation as it may prevent the placement of the electrodes. Therefore, early diagnosis and adequate follow-up are pivotal for enabling timely and effective prevention and treatment.[12]

From the Postgraduate Program in Medicine: Surgical Sciences (A.K.S., J.L.), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil; Department of Otolaryngology, Head & Neck Surgery (N.K.Y., T.S., S.C., R.D.C.M.), University of Minnesota, Minneapolis, Minnesota, U.S.A.; Department of Internal Medicine, Faculty of Veterinary Medicine (N.K.Y.), Ankara University, Ankara, Türkiye; and the Department of Otorhinolaryngology (T.S.), Showa University Fujigaoka Hospital, Yokohama, Japan.

Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on August 26, 2024.

This project was funded by NIH NIDCD U24 DC020851-02, International Hearing Foundation, Lions 5 m International and Scientific and Technological Research Council of Türkiye (TUBITAK) Scholarship, and financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil* (CAPES)—Finance Code 001.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Rafael da Costa Monsanto, MD, PhD, University of Minnesota, Lion's Research Building, 2001 6th St SE, Room 210, Minneapolis, MN 55455. Email: rafaelmonsanto@hotmail.com

DOI: 10.1002/lary.31759

The literature concerning factors that correlate with the severity of the intra-cochlear inflammation and subsequent hearing outcomes in meningitis is scarce. Previous studies suggested a potential link between OM and poorer hearing outcomes in cases of meningitis.[13,14] However, further confirmation of this association is needed. This gap in knowledge creates a significant void in our understanding of the underlying pathophysiological mechanisms of cochlear ossification and subsequent hearing loss. Consequently, it constrains our ability to develop improved screening and early diagnosis techniques, as well as the development of targeted therapies aimed at preventing its occurrence. Otopathological studies provide a unique opportunity to investigate these factors in temporal bones (TBs) from patients who had meningitis.

To test the hypothesis that the otogenic route in meningitis cases is associated with more severe inner ear inflammation and higher risks of cochlear ossification, we employed a comprehensive histopathological study protocol. The main goal is to assess the patterns and severity of inner ear changes in patients with meningitis by comparing otogenic and meningogenic labyrinthitis cases. Identifying unique patterns associated with each route of infection could enhance diagnostic criteria and facilitate the development of targeted therapies aimed at mitigating inflammatory changes, ultimately reducing the likelihood of hearing loss and irreversible ossification.

MATERIALS AND METHODS

From the archival TB collection at the Paparella Otopathology & Pathogenesis Laboratory, University of Minnesota, we selected TBs from donors with a history of meningitis. Human TB studies utilizing our archival collection are Institutional Review Board-exempt (ID:STUDY00003249). All of the archival TBs had been removed at autopsy and processed using a standard protocol.[15] Briefly, all TBs were fixed in 10% buffered formalin, decalcified with ethylenediaminetetraacetic acid, dehydrated with alcohol and embedded in celloidin. Sections in the horizontal plane at a thickness of 20 μm were made, and every 10th section was stained using hematoxylin–eosin.

Inclusion criteria were a documented history of meningitis and histopathological evidence of labyrinthitis. Exclusion criteria were (1) pre-existing auditory or vestibular dysfunction prior to meningitis, such as cochlear otosclerosis and Meniere's disease, (2) a history of middle or inner ear surgery, including mastoidectomy and cochlear implantation, (3) a history of metastatic disease, (4) a history of chemotherapy or radiotherapy, and (5) TBs exhibiting severe postmortem changes.

Specimens were grouped into two categories (otogenic and meningogenic) based on the route of infection: (1) otogenic: medical records indicating middle ear infection as the etiology of meningitis and/or those demonstrating histopathological evidence of acute or chronic middle ear inflammation (such as purulent material, mucosal thickening, granulation tissue or cholesteatoma) (Fig. 1); (2) meningogenic: cases lacking a medical history of OM and devoid of any pathological middle ear findings were classified as meningogenic labyrinthitis.

To determine the sites of lesion and severity of the inner ear changes, we scrutinized the TBs under light microscopy. We assessed the samples for the presence of inflammatory cells and pathologic changes using qualitative and semi-quantitative methods.

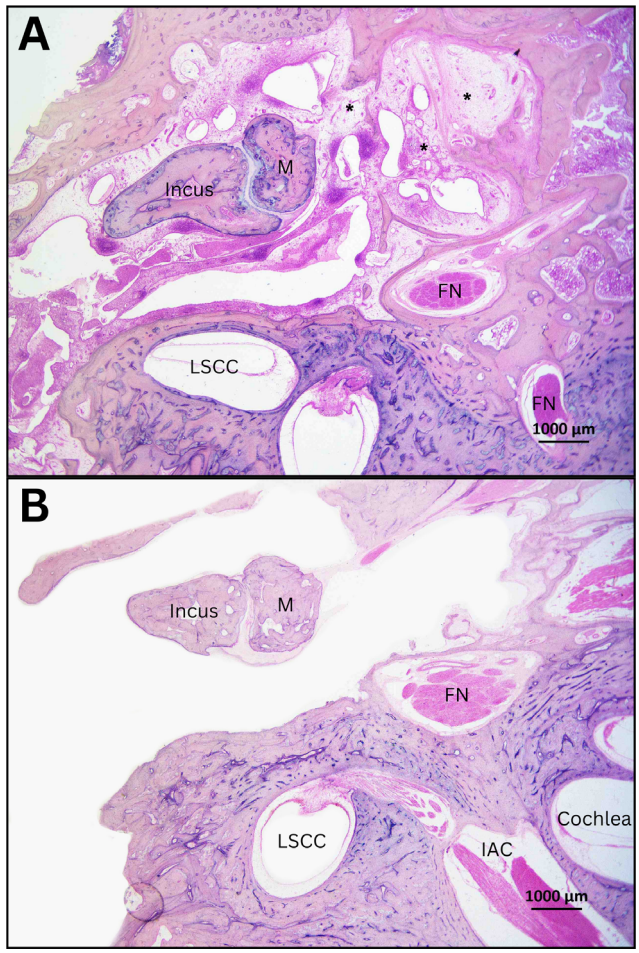

Fig. 1. Two representative temporal bone sections showing middle ear changes. (A) Otogenic meningitis case displaying middle ear changes, like thickened mucosa, granulation tissue (*), purulent effusion, and polymorphonuclear infiltration. (B) Meningogenic case with no significant finding in the middle ear. FN = facial nerve; IAC = internal auditory canal; LSCC = lateral semicircular canal; M = malleus. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

The presence of labyrinthitis was classified as "localized" (confined to the area of scala tympani adjacent to the cochlear aqueduct and the round window membrane—RWM) or "generalized" (inflammatory changes seen throughout the labyrinth).[16] The inflammatory fluid within the labyrinth was further characterized as "serous" (eosinophilic precipitate without inflammatory cells) or "purulent" (polymorphonuclear neutrophils). Cases exhibiting generalized purulent labyrinthitis were additionally classified into three subgroups: (1) acute, purulent effusion followed by the formation of serofibrinous precipitates filling the perilymphatic spaces; (2) fibrous, fibroblastic proliferation and angiogenesis; and (3) cochlear ossification, being early signs (such as purulent effusion with serofibrinous precipitates and fibroblastic proliferation filling the perilymphatic spaces) or established (new bone formation).[17]

We analyzed the presence of endolymphatic hydrops, which was classified (when present) in slight, moderate or severe.[18] Loss of cochlear and vestibular hair cells was assessed using a semi-quantitative scale (mild, moderate, or severe).[19] Qualitative changes affecting the SV (edema, atrophy, and/or concretions) were assessed.[8] We analyzed for the loss of fibrocytes in the

spiral ligament (SL) and classified according to the severity of findings in normal, mild, moderate, or severe.[20] We evaluated the presence of increased thickness of the RWM, as well as the presence of inflammatory cells or fluid in the basal turn.[21] The endolymphatic duct and sac, as well as the cochlear aqueduct, were scrutinized for the presence of histologic changes such as the presence of inflammatory cells.[22,23]

Statistical analyses were performed using the IBM SPSS (v29.0) software. Descriptive statistics (means, standard deviations, medians, counts, and percentages for categorical variables) were used to summarize the outcomes. Nominal variables were analyzed using chi-square with or without pairwise z-tests and Bonferroni adjustment, and ordinal variables with one-way ANOVA and Tukey post hoc. Results were considered statistically significant when the p value was less than 0.05.

RESULTS

Our final group of meningitis cases comprised 36 TBs from 19 donors (meningogenic, $n = 15$ TBs; otogenic, $n = 21$ TBs) (Table I, Figures S1 and S2). The age of death ranged from 7 days to 86 years (mean, 39.5 ± 32.2 years) in the meningogenic group and from 4.8 months to 64 years (mean, 13.2 ± 22.5 years) in the otogenic group. The time from the diagnosis of meningitis to death ranged from 1 day to 2.4 years (mean, 137.1 ± 328 days) in meningogenic patients and from 1 to 74 days (mean, 11.5 ± 21 days) in otogenic patients. Among the 11 donors of the otogenic group, 10 had bilateral middle ear changes. In those cases, it was not possible to identify what ear (or if both) caused the labyrinthitis, as findings were similar in both ears.

Labyrinthitis Pattern

The otogenic group exhibited a higher rate of generalized labyrinthitis compared with the meningogenic group (100% and 53%, respectively; $p < 0.001$) (Table II). Within the otogenic group, labyrinthitis was purulent in 19 cases and serous in 2 TBs. Among the eight meningogenic cases with generalized labyrinthitis, six were purulent and two were serous. In the remaining seven TBs with localized labyrinthitis, inflammatory fluid was purulent in four cases and serous in three cases.

Signs of inflammation in otogenic cases were more pronounced in the scala tympani (13 TBs, 62%), scala vestibuli (10 TBs, 48%), and the modiolus (12 TBs, 57%). We observed a higher prevalence of the presence of inflammatory cells in otogenic cases compared with the meningogenic group ($p = 0.026$). In meningogenic cases, eosinophilic precipitate was observed in the scala tympani in six TBs (40%), scala vestibuli in four TBs (27%), and in the modiolus in three TBs (20%) (Fig. 2).

Labyrinthitis Ossificans

Early signs of labyrinthitis ossificans were exclusively identified in otogenic cases (9 TBs; 43%; $p = 0.003$; Table II; Fig. 3). In cerebrospinal fluid analyses of cases with signs of labyrinthitis ossificans, the identified causative agents were *Streptococcus pneumoniae* (6 cases; 66.6%) and *Haemophilus influenzae* (3 cases; 33.3%). We did not find a significant correlation between the type of bacteria or positive or negative Gram staining and the presence of signs of ossification ($p > 0.05$).

Internal Auditory Canal

Our data revealed that otogenic cases had higher prevalence of the severe presence of inflammatory cells in the internal auditory canal (IAC) compared with the meningogenic group (otogenic group: 14 TBs, 67%; meningogenic group: 1 TB, 7%; $p = p.002$) (Table II; Figures S1 and S2).

Round Window Membrane

The RWM was thickened in all otogenic cases, especially in those with early signs of ossification; no significantly increased RWM thickness was observed in meningogenic cases.

Lateral Wall

SV edema was identified in 16 TBs (76%) within the otogenic group and in 9 TBs (60%) of the meningogenic group ($p = 0.298$). SV atrophy was seen in 6 TBs (29%) of the otogenic group and in 1 TB (7%) of the meningogenic group ($p = 0.102$) (Table III).

All TBs from both groups exhibited loss of SL fibrocytes affecting at least one cochlear turn (Fig. 4). Otogenic cases exhibited a higher prevalence loss of fibrocytes, particularly in the middle turn ($p = 0.014$). The loss of fibrocytes in meningogenic cases tended to increase from the basal to the apical turn ($p = 0.030$). Conversely, in otogenic cases, the loss of fibrocytes was evenly distributed across all cochlear turns ($p = 0.705$; Table III).

Cochlear and Vestibular Aqueducts

In otogenic cases, the proportion of cases exhibiting severe inflammation in the cochlear aqueduct was significantly higher (otogenic, 7 TBs, 33%; meningogenic, none; $p = 0.014$). We found a higher prevalence of inflammatory cells in the endolymphatic sac of TBs in the otogenic group ($p < 0.001$), while no significant difference was observed in the endolymphatic duct ($p = 0.235$) (Table II).

Hair Cell Loss and Hydrops

Due to processing artifacts, analysis of the organ of Corti was possible only in 12 TBs of the meningogenic group and in 7 TBs of the otogenic group. We did not find significant differences in the loss of cochlear hair cells between groups (otogenic, 3TBs; meningogenic, 6TBs; $p = 0.079$). Slight cochlear hydrops were seen in three TBs from each group ($p = 0.650$). We found more severe loss of vestibular hair cells in the otolithic organs in the meningogenic group as compared with the otogenic group ($p = 0.019$; Fig. 5). In both groups, all semicircular canals were normal or presented mild hair cell loss.

TABLE I.
Demographic Data From the Temporal Bone Donors.

	Case	Side	Age of Death (Years)	Sex	Agent	Age at Time of Meningitis	Time From Meningitis to Death
Meningogenic group	1	R and L	47	Male	n/a	47 years	8 days
	2	R and L	3	Female	*Streptococcus pneumoniae*	7 months	2.4 years
	3	R and L	44	Male	*Pseudomonas aeruginosa*	44 years	3 days
	4	R and L	41	Male	*Cryptococcus neoformans*	41 years	1 day
	5*	R and L	79	Female	n/a*	n/a*	n/a*
	6	L	86	Male	*Streptococcus pneumoniae*	86 years	17 days
	7	R and L	16	Male	*Staphylococcus* spp	16 years	48 days
	8	R and L	0.02	Male	n/a	4 days	3 days
Otogenic group	9	R and L	0.4	Male	*Streptococcus pneumoniae*	2 months	74 days
	10	R and L	1.9	Male	*Haemophilus influenzae*	1.9 year	8 days
	11	R and L	1.8	Male	*Haemophilus influenzae*	1.8 year	2 days
	12	R and L	2	Male	*Haemophilus influenzae*	2 years	1 days
	13	R and L	24	Male	*Streptococcus pneumoniae*	24 years	8 days
	14	R	48	Male	*Peptostreptococcus anaerobius*	48 years	6 days
	15	R and L	1.6	Female	*Streptococcus pneumoniae*	1.6 year	4 days
	16	R and L	0.4	Male	*Streptococcus pneumoniae*	4.8 months	10 days
	17	R and L	0.8	Male	*Haemophilus influenzae*	9.7 months	2 days
	18	R and L	0.6	Male	*Haemophilus influenzae*	7.3 months	3 days
	19	R and L	64	Male	*Streptococcus pneumoniae*	64 years	8 days

For case number 5 (*), although it was not available the exact time from meningitis to death, the cause of death was registered as meningitis, and the histopathology shows clear signs of acute infection.
L = left; n/a = not available; R = right.

DISCUSSION

Our findings suggest that otogenic labyrinthitis leads to more pronounced inner ear inflammation compared with meningogenic cases. Meningitis can result in profound hearing loss and cochlear ossification, which can impede cochlear implant placement.[11] Thus, comprehending the pathophysiological mechanisms linked to meningitis-related labyrinthitis is crucial for developing screening, early diagnosis, and treatment strategies aimed at preventing these complications.

These findings are likely attributed to the distinct routes of bacterial translocation to the inner ear. In otogenic cases, the close anatomical proximity and the permeability of the RWM create conducive conditions for local bacterial infiltration, generating a generalized cochlear inflammation and damage, as well as sensorineural hearing loss.[24,25] While theoretically, an increased thickness of the RWM acts as a barrier, reducing membrane permeability, this thickening might have happened after bacteria entered the inner ear, possibly due to prolonged OM.[26] Additionally, in otogenic cases, meningitis can occur through bacterial translocation to the meninges via areas of bony dehiscence, such as Schuknecht's canal.[8] Based on our observations in otogenic cases, it appears that the cochlear aqueduct can also serve as a route for meningitis in this group, as we detected a significant number of inflammatory cells in that location.

Regarding meningogenic cases, it is understood that the cochlear aqueduct primarily serves as the route for infection spread from the meninges to the inner ear.[10] However, temporal bone studies also suggest that the modiolus could be a potential route for pathogens. In this scenario, pathogens may enter the IAC through the porus acusticus and subsequently reach the modiolus via the cochlear nerve aperture, traveling along with the nerve fibers of the cochlear nerve.[27] Our findings of inflammatory cells within the modiolus support this hypothesis. Furthermore, we did not observe a significant amount of bacteria or inflammatory cells in the endolymphatic sac, in the meningogenic group. Although the intimate anatomical relationships between the sac and the meninges would indicate otherwise, our findings align with previous research, also showing no involvement of the endolymphatic sac in meningitis cases, potentially due to its robust immune function.[10,27,28] Instead, it appears that infection spreads to the inner ear through the cochlear aqueduct or the modiolus.[28]

We observed widespread cochlear changes affecting both groups, although the patterns of lesions varied. One notable finding was that only temporal bones from the otogenic group exhibited signs of early cochlear ossification, suggesting that otogenic cases are more predisposed to developing ossification. As most donors passed away shortly after meningitis diagnosis, this may indicate a progression toward ossification. Also, the short time between infection and death reduces the confounding bias of other otologic events that could damage the labyrinth. In cases of meningitis-associated labyrinthitis, cochlear

TABLE II.
A Summary of the Inner Ear Histopathological Findings in Temporal Bones With Meningogenic and Otogenic Labyrinthitis.

	Labyrinthitis Pattern*		IAC (Inflammatory Cells Presence)*			Fibro-Ossification Stage*	Cochlear Aqueduct (Inflammatory Cells Presence)*			Endolymphatic Duct (Inflammatory Cells Presence)			Endolymphatic Sac (Inflammatory Cells Presence)*		
	n (%)		*n* (%)				*n* (%)			*n* (%)			*n* (%)		
	Generalized*	Localized*	Mild	Mod.	Severe*	*n* (%)	Mild	Mod.	Severe*	Mild	Mod.	Severe	Mild	Mod.*	Severe
Meningogenic group $n = 15$	8 (53%)	7 (47%)	3 (20%)	7 (47%)	1 (7%)	0	7 (47%)	1 (7%)	0	5 (33%)	6 (40%)	0	5 (33%)	0	0
Otogenic group $n = 21$	21 (100%)	0	2 (10%)	5 (24%)	14 (67%)	Acute: 8 (38%) Fibrous: 1 (5%)	3 (14%)	5 (24%)	7 (33%)	5 (24%)	11 (52%)	3 (14%)	4 (19%)	13 (62%)	0

*Sites of lesion where the difference between groups was statistically significant ($p < 0.05$); *n*, number of temporal bones; %, percentage using the total number of temporal bones in each group as denominator.
IAC = internal auditory canal; Mod = moderate.

Fig. 2. Representative temporal bone sections showing cochlear changes. (A) Otogenic meningitis case; arrows: eosinophilic precipitate; *, purulent material. (B) Meningogenic case; arrows: eosinophilic precipitate. SL = spiral ligament; SM = scala media. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

fibrosis typically begins around 2 weeks, with ossification starting within 2 months.[29] In otogenic cases, the direct penetration of bacteria and inflammatory products induces strong inflammation in the inner ear, thus promoting ossification. Conversely, meningogenic cases have a lower bacterial count reaching the inner ear due to bony barriers. Nonetheless, other authors reported cochlear ossification in meningogenic cases as well.[30]

The increased inflammatory changes and higher prevalence of ossification signs we observed have significant clinical implications. Previous research indicates that, despite one third of all meningitis cases being of otogenic origin, only 54% of patients with suspected meningitis receive an otoscopic examination.[14] Based on our findings, it is crucial to promptly identify patients with suspected otogenic meningitis and systematically assess them for hearing loss to ensure timely cochlear implantation. From a clinical perspective, considering the potential risks of severe cochlear inflammation and ossification associated with labyrinthitis, regardless of its origin, it is essential for surgeons to follow screening protocols,

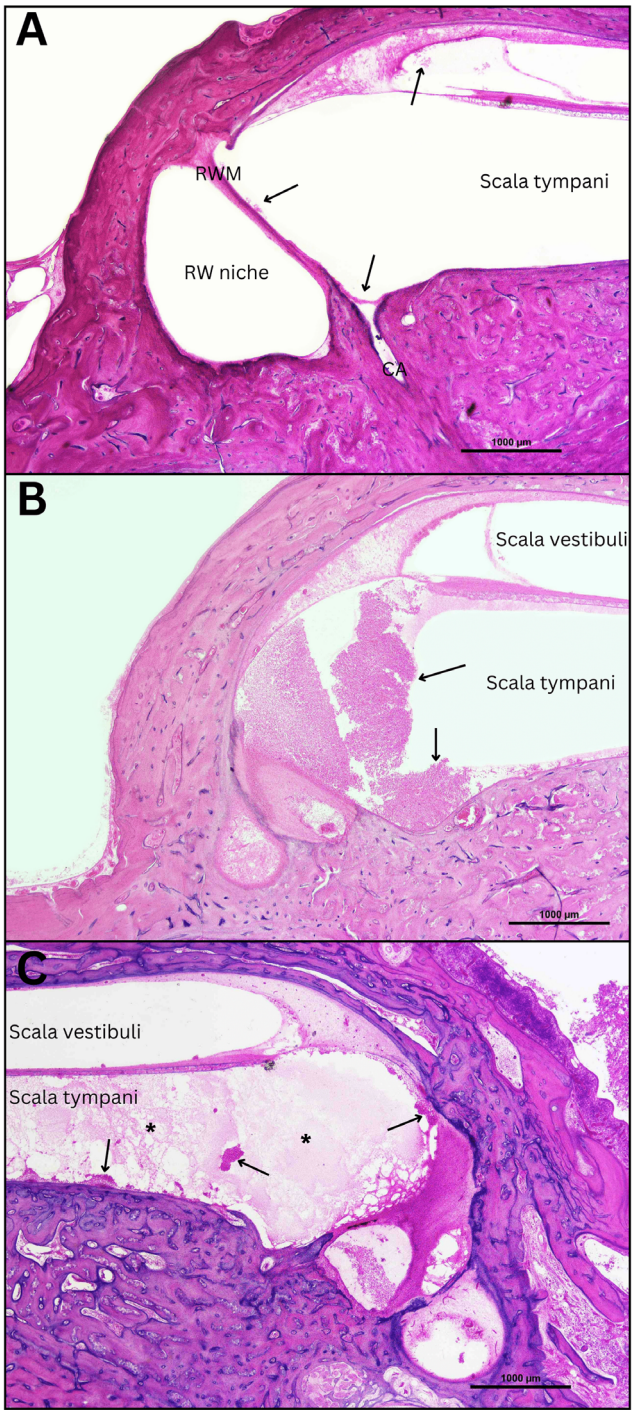

Fig. 3. Three representative temporal bone sections showing different patterns of purulent labyrinthitis. (A) Localized labyrinthitis; arrows: polymorphonuclear cells. (B) Generalized labyrinthitis, acute stage; arrows: polymorphonuclear cells. (C) Generalized labyrinthitis, fibrous stage; arrows: polymorphonuclear cells; *: fibrous tissue. CA = cochlear aqueduct; RW = round window; RWM = round window membrane. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

conduct thorough physical examinations to detect possible otogenic cases, and ensure proper audiological follow-up to minimize complications. Future clinical studies could further refine pathology-oriented practice guidelines for managing both meningogenic and otogenic cases.

We observed a high rate of SV changes in both groups. Given that the SV has a high metabolic rate and plays a crucial role in inner ear homeostasis, its sensitivity to inflammatory damage may be explained by these factors.[31] SV abnormalities can disrupt both the regulatory mechanisms of the blood–labyrinth barrier and the ionic regulation of the endolymph, impairing the mechanisms of sound transmission.[32] Additionally, it has been shown that the SV might be a route of hematogenic labyrinthitis in meningogenic cases.[10] As cochlear findings were less severe in meningogenic cases, we hypothesize that either the SV route is less frequent as compared with the aqueduct/modiolus routes, or that the blood–labyrinth barrier may provide protection against substantial penetration of bacterial products to the cochlea.

We observed distinct patterns of SL fibrocyte loss between the groups: otogenic cases showed fibrocyte loss throughout all cochlear turns, while in meningogenic cases, fibrocyte loss increased from the basal to the apical turn. These findings likely reflect differing patterns of intracochlear inflammation. The uniform and more pronounced fibrocyte loss in otogenic cases suggests more severe intracochlear inflammation. This is likely due to the direct translocation of inflammatory mediators and bacterial products from the middle ear through the RWM. Given the spiral ligament's crucial role in generating endolymphatic potential and in stress-response pathways within the inner ear, cases of more severe fibrocyte damage, such as otogenic labyrinthitis, could represent a greater risk of hearing loss and cochlear ossification. Although we can only speculate on why the apical turn is more affected in meningogenic cases, we have proposed two potential explanations: (1) The volume of the SL decreases from the base to the apex, making fibrocyte loss more noticeable in the apical turn initially[33]; or (2) a different route of infection spread might selectively affect specific types of SL fibrocytes and areas.[34,35] Further studies could provide insight into how the route of labyrinthitis infection is linked to specific damage in the SL.

An interesting finding was that meningogenic cases had increased loss of vestibular hair cells in the otolithic organs. Although initially counterintuitive, it is possible that the direct penetration of the inflammatory mediators through the vestibular nerve canals (as opposed to the cochlea in otogenic cases) triggers a local inflammatory response.[8] The findings of Pauna et al. corroborate our hypothesis by demonstrating translocation of bacteria and inflammatory cells through the cochlear nerve canal into the modiolus.[19] Although the clinical significance of these findings remains uncertain, past studies have shown that bacterial meningitis in children correlates with chronic vestibular impairment in up to 10.5% of cases and may result in delayed posturomotor development.[36] As no previous study has compared vestibular impairment between meningogenic and otogenic meningitis cases, future clinical research could provide further insight into whether our observation of heightened

TABLE III.
Stria Vascularis and Spiral Ligament Findings in Temporal Bones With Meningogenic and Otogenic Labyrinthitis.

		Stria Vascularis (Qualitative Changes)		Spiral Ligament (Loss of Fibrocytes)*		
		n (%)		*n* (%)		
		Edema	Atrophy	Mild	Moderate	Severe
Meningogenic group $n = 15$	Basal turn	7 (47%)	0	4 (27%)	7 (47%)	0
	Middle turn	9 (60%)	1 (7%)	1 (7%)	8 (53%)	4 (27%)
	Apical turn	7 (47%)	1 (7%)	2 (13%)	5 (33%)	6 (40%)
Otogenic group $n = 21$	Basal turn	15 (71%)	6 (29%)	6 (29%)	6 (29%)	1 (5%)
	Middle turn	16 (76%)	6 (29%)	12 (57%)	6 (29%)	1 (5%)
	Apical turn	15 (71%)	6 (29%)	11 (52%)	6 (29%)	2 (10%)

*Sites of lesion where difference between groups was statistically significant ($p < 0.05$); *n*, number of temporal bones; %, percentage using the total number of temporal bones in each group as denominator.

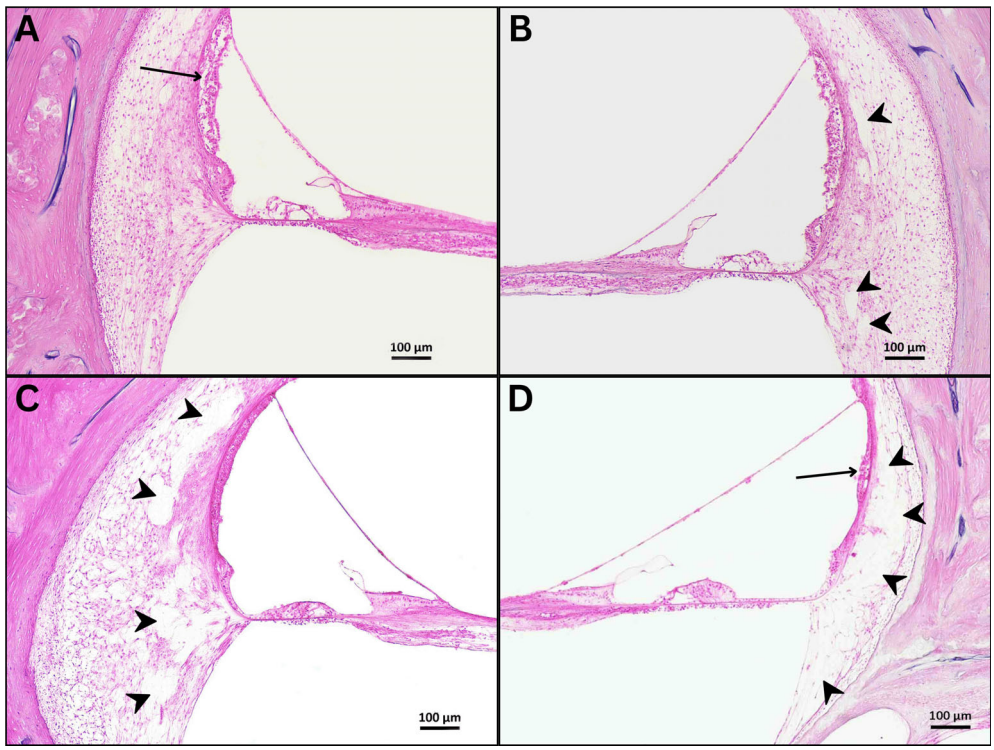

Fig. 4. Representative temporal bone sections showing the visual scale used to assess changes in the spiral ligament (SL) and stria vascularis (SV). (A) Normal SL; arrow: SV with edema. (B) SL with mild loss of fibrocytes; arrow head: areas of loss of fibrocytes. (C) SL with moderate loss of fibrocytes; arrow head: areas of loss of fibrocytes; (D) SL with severe loss of fibrocytes; arrow: atrophic SV; arrow head: areas of loss of fibrocytes. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

vestibular damage in meningogenic cases translates to vestibular dysfunction in this specific patient subset.

This study has limitations. The quantity of medical information from donors is restricted by the availability of their medical records in our files. Additionally, because the individuals whose bones were included in our study passed away shortly after contracting meningitis, no hearing tests were accessible. The limited number of specimens from donors limited the possibilities for comparative analysis and increased the heterogeneity of the samples. It is also possible that—because of antibiotic use—some cases that were otogenic cases were classified as meningogenic due to resolution of the middle ear infection. However, this is unlikely because the medical documentation allowed us to rule out otitis media; also, because of the short period between diagnosis and death in those cases, it is unlikely that the inflammatory changes would be completely resolved with the antibiotic use. It is important to note that one case in the meningogenic group involved a fungal infection, and in some instances, the pathogen was not isolated. However, the significant presence of polymorphonuclear cells indicated a bacterial infection in these cases. Therefore, although most cases were clearly associated with bacterial

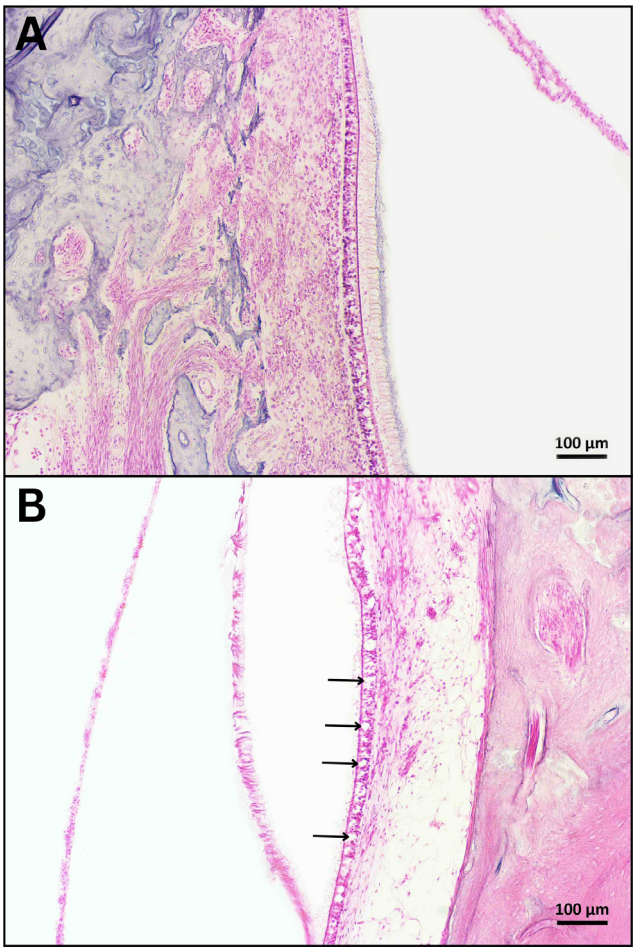

Fig. 5. Representative sections showing the semi-quantitative assessment of loss of vestibular hair cells in the saccule. (A) Normal macula. (B) Mild loss of hair cells; arrows: areas of cell loss. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

infections, the studied cohort is not homogeneous with respect to the causative agents. Despite the limitations, this study provides histologic evidence of the progression patterns of inner ear inflammation in different routes of meningitis. Our findings will underpin future clinical studies dedicated to the creation of improved diagnostic criteria, application of prevention techniques, and development of targeted, noninvasive therapies dedicated to controlling the inflammatory changes, reducing the chances of hearing loss or cochlear ossification secondary to meningitis.

CONCLUSION

Our findings revealed that otogenic cases are associated with more severe cochlear changes, while meningogenic cases are associated with more severe vestibular damage. Our study offers insights into the underlying mechanisms behind distinct inflammation patterns that can be translated in the development of preventative and treatment strategies in the future.

BIBLIOGRAPHY

1. Boeddha NP, Schlapbach LJ, Driessen GJ, et al. Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS). *Crit Care*. 2018;22(1):143.
2. GBD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(12):1061-1082.
3. Worsøe L, Cayé-Thomasen P, Brandt CT, Thomsen J, Østergaard C. Factors associated with the occurrence of hearing loss after pneumococcal meningitis. *Clin Infect Dis*. 2010;51(8):917-924.
4. Lucas MJ, Brouwer MC, van de Beek D. Neurological sequelae of bacterial meningitis. *J Infect*. 2016;73(1):18-27.
5. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(5):317-328.
6. Lempinen L, Karppinen M, Pelkonen T, et al. Otitis media-associated bacterial meningitis in children in a low-income country. *Pediatr Infect Dis J*. 2019;38(8):791-797.
7. Bjar N, Hermansson A, Gisselsson-Solen M. How common is otogenic meningitis? A retrospective study in southern Sweden over 18 years. *Infection*. 2024;52(4):1377-1384. https://doi.org/10.1007/s15010-024-02195-z.
8. Schachern PA, Paparella MM, Hybertson R, Sano S, Duvall AJ 3rd. Bacterial tympanogenic labyrinthitis, meningitis, and sensorineural damage. *Arch Otolaryngol Head Neck Surg*. 1992;118(1):53-57.
9. Klein M, Koedel U, Kastenbauer S, Pfister HW. Nitrogen and oxygen molecules in meningitis-associated labyrinthitis and hearing impairment. *Infection*. 2008;36(1):2-14.
10. Møller MN, Brandt C, Østergaard C, Caye-Thomasen P. Bacterial invasion of the inner ear in association with pneumococcal meningitis. *Otol Neurotol*. 2014;35(5):e178-e186.
11. Becker TS, Eisenberg LS, Luxford WM, House WF. Labyrinthine ossification secondary to childhood bacterial meningitis: implications for cochlear implant surgery. *AJNR Am J Neuroradiol*. 1984;5(6):739-741.
12. Bille J, Ovesen T. Cochlear implant after bacterial meningitis. *Pediatr Int*. 2014;56(3):400-405.
13. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med*. 2004;351(18):1849-1859.
14. Persson F, Bjar N, Hermansson A, Gisselsson-Solen M. Hearing loss after bacterial meningitis, a retrospective study. *Acta Otolaryngol*. 2022;142(3-4):298-301.
15. Monsanto R d C, Penido N d O, Uchiyama M, Schachern P, Paparella MM, Cureoglu S. Quantitative assessment of cochlear and vestibular ganglion neurons in temporal bones with chronic otitis media. *Eur Arch Otorhinolaryngol*. 2021;278(2):331-338.
16. Joglekar S, Morita N, Cureoglu S, et al. Cochlear pathology in human temporal bones with otitis media. *Acta Otolaryngol*. 2010;130(4):472-476.
17. Paparella MM, Sugiura S. The pathology of suppurative labyrinthitis. *Ann Otol Rhinol Laryngol*. 1967;76(3):554-586. https://cir.nii.ac.jp/crid/1572261549272414592.
18. Cureoglu S, Schachern PA, Paul S, Paparella MM, Singh RK. Cellular changes of Reissner's membrane in Meniere's disease: human temporal bone study. *Otolaryngol Head Neck Surg*. 2004;130(1):113-119.
19. Pauna HF, Knoll RM, Lubner RJ, et al. Histopathological changes to the peripheral vestibular system following meningitic labyrinthitis. *Laryngoscope Investig Otolaryngol*. 2020;5(2):256-266.
20. Cureoglu S, Schachern PA, Paparella MM, Lindgren BR. Cochlear changes in chronic otitis media. *Laryngoscope*. 2004;114(4):622-626.
21. Keskin Yılmaz N, Albasan H, Börkü MK, Paparella MM, Cüreoğlu S. Three-dimensional analysis of round window membrane in the chinchilla model with acute otitis media induced with *Streptococcus pneumoniae* 7F. *Turk Arch Otorhinolaryngol*. 2021;59(1):43-48.
22. Plantenga KF, Browning GC. The vestibular aqueduct and endolymphatic sac and duct in endolymphatic hydrops. *Arch Otolaryngol*. 1979;105(9):546-552.
23. Cayé-Thomasen P, Worsøe L, Brandt CT, et al. Routes, dynamics, and correlates of cochlear inflammation in terminal and recovering experimental meningitis. *Laryngoscope*. 2009;119(8):1560-1570.
24. Juhn SK, Jung MK, Hoffman MD, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. *Clin Exp Otorhinolaryngol*. 2008;1(3):117-138.
25. Juhn SK, Jung TT, Lin J, Rhee CK. Effects of inflammatory mediators on middle ear pathology and on inner ear function. *Ann N Y Acad Sci*. 1997;830:130-142.
26. Sahni RS, Paparella MM, Schachern PA, Goycoolea MV, Le CT. Thickness of the human round window membrane in different forms of otitis media. *Arch Otolaryngol Head Neck Surg*. 1987;113(6):630-634.
27. Merchant SN, Gopen Q. A human temporal bone study of acute bacterial meningogenic labyrinthitis. *Am J Otol*. 1996;17(3):375-385.
28. Møller MN, Brandt C, Østergaard C, Caye-Thomasen P. Endolymphatic sac involvement in bacterial meningitis. *Eur Arch Otorhinolaryngol*. 2015;272(4):843-851.
29. Xu HX, Joglekar SS, Paparella MM. Labyrinthitis ossificans. *Otol Neurotol*. 2009;30(4):579.
30. Trakimas DR, Knoll RM, Castillo-Bustamante M, Kozin ED, Remenschneider AK. Otopathologic analysis of patterns of postmeningitis

labyrinthitis ossificans. *Otolaryngol Head Neck Surg*. 2021;164(1): 175-181.
31. Ciuman RR. Stria vascularis and vestibular dark cells: characterisation of main structures responsible for inner-ear homeostasis, and their pathophysiological relations. *J Laryngol Otol*. 2009;123(2):151-162.
32. Juhn SK, Rybak LP, Prado S. Nature of blood-labyrinth barrier in experimental conditions. *Ann Otol Rhinol Laryngol*. 1981;90(2 Pt 1):135-141.
33. Flood LM. Schuknecht's pathology of the ear. *J Laryngol Otol*. 2013; 127(3):329.
34. Peeleman N, Verdoodt D, Ponsaerts P, Van Rompaey V. On the role of fibrocytes and the extracellular matrix in the physiology and pathophysiology of the spiral ligament. *Front Neurol*. 2020;11:580639.
35. Spicer SS, Schulte BA. The fine structure of spiral ligament cells relates to ion return to the stria and varies with place-frequency. *Hear Res*. 1996; 100(1-2):80-100.
36. Wiener-Vacher SR, Obeid R, Abou-Elew M. Vestibular impairment after bacterial meningitis delays infant posturomotor development. *J Pediatr*. 2012;161(2):246-251.e1.