



## ORIGINAL RESEARCH

## Cochlear turns measurements in patients with meningitis: A histopathological study

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## Abstract

**Objective:** To demonstrate the cochlear turns area changes among patients with a history of meningitis, through otopathologic study.

**Methods:** We performed an analysis of the area of the bony cochlear turns and the cochlear lumen of the horizontal sections containing the modiolus and the area of the basal turn at the level of round window, in temporal bones obtained from patients with a history of meningitis and compared to a nondiseased control group.

**Results:** The mean area of the bony walls and the lumen of all cochlear turns are reduced within the meningitis group. Patients who presented a time from the diagnosis of meningitis to death longer than 30 days had a significant reduction in the cochlear turns area, as compared to the control group.

**Conclusion:** Future studies may further correlate audiologic outcomes, cochlear volume, and cochlear area among patients with meningitis.

## KEYWORDS

cochlear turns, labyrinthitis ossificans, meningitis, otopathology, temporal bone

## 1 | INTRODUCTION

Bacterial meningitis is a major cause of profound sensorineural hearing loss in children, with prevalence ranging from 60% to 90%.<sup>1</sup> Bacterial infection in the subarachnoid space usually reaches the cochlea through the cochlear aqueduct but may also reach the cochlea through adjacent structures, often causing irreversible damage within inner ear structures.<sup>1,2</sup> As a result, labyrinthitis ossificans can be seen in the otic capsule in response to the inflammatory process.<sup>2</sup>

Cochlear ossification is known as a pathological process. Preoperative imaging by computed tomography (CT) is mandatory for preoperative planning. A retrospective review of preoperative CT scans

performed among 34 candidates with bilateral hearing loss following meningitis found cochlear ossification in 35% of them.<sup>3</sup> Using a high-resolution CT scan of 15 ears, from 13 patients with profound hearing loss following meningitis, Ichikawa et al found soft tissue, partial bony occlusion, and complete bony occlusion in 3, 2, and 6 ears, respectively.<sup>4</sup>

Despite of the tomographic demonstration of labyrinthitis ossificans, the literature is scarce to demonstrate, histopathologically, the differences of bony cochlear area and cochlear lumen area among patients with a history of meningitis. Therefore, in this otopathologic study, our aim is to present cochlear area measurements along the modiolus and round window in a group of patients with a history of meningitis.

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## 2 | MATERIALS AND METHODS

### 2.1 | Temporal bones

The human temporal bones for this study were obtained at the Otopathology Laboratory, University of Minnesota, Minneapolis, Minnesota. Immediately after removal, the temporal bones were placed in 10% buffered-formalin, decalcified with ethylenediaminetetraacetic acid, dehydrated in graded concentrations of alcohol, and embedded in celloidin. Each bone was serially sectioned in the horizontal plane at a thickness of 20  $\mu\text{m}$ . Every 10th section was stained with hematoxylin and eosin, and then evaluated using light microscopy.

The following two groups of temporal bones were studied: (a) meningitis, and (b) control group with no middle ear disease and no history of infectious central nervous system disease.

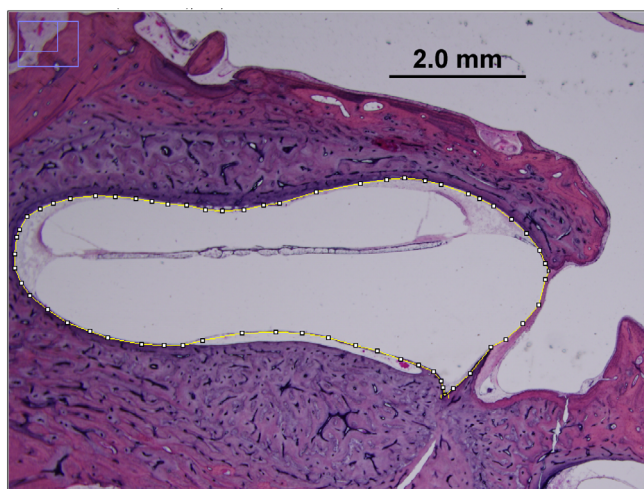
We excluded temporal bones from donors who had any of the following: history of acute or chronic otitis media; tumors affecting the middle or the inner ear; hematologic diseases; irradiation of the head and neck; chemotherapy; a history of aminoglycoside use (either

topical or systemic); otologic surgery; Meniere's disease; clinical otosclerosis; or systemic autoimmune disease. In addition, we excluded temporal bones affected by processing artifacts. Then, we further screened the remaining samples to ensure integrity of the cochlea (organ of Corti, stria vascularis, and Rosenthal canal).

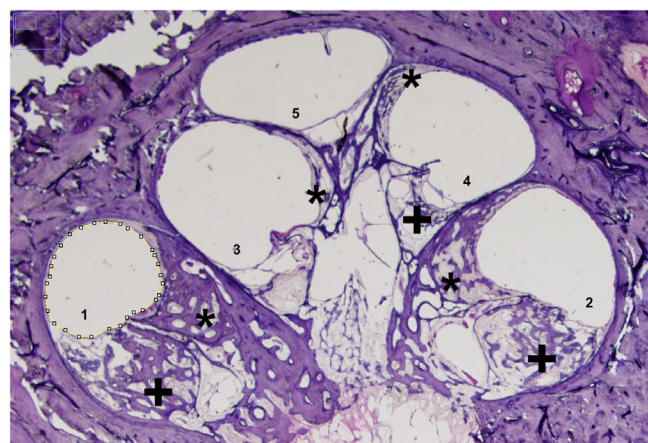
The authors were responsible for scrutinizing the temporal bones and were blinded from the group that each temporal bone belongs to and some patient information, including sex, age, and medical history.

### 2.2 | Cochlear system

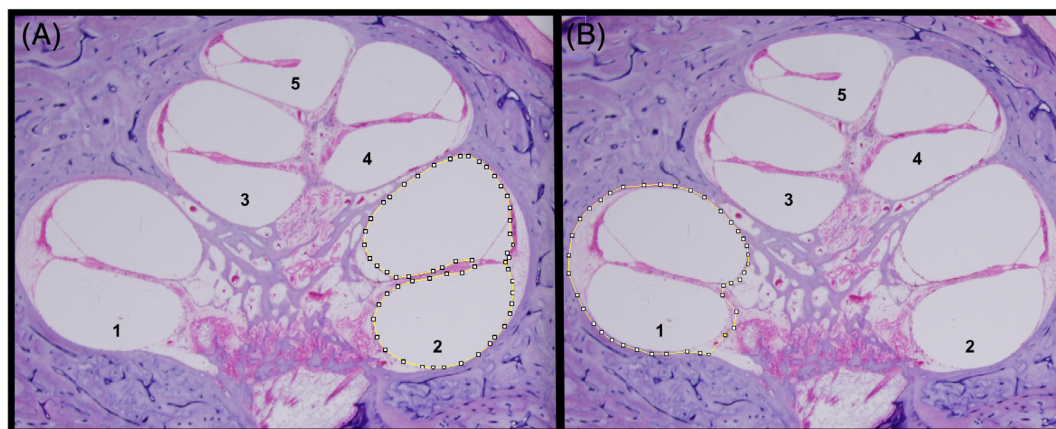
We assessed the presence or absence of pathologic changes affecting the cochlea, such as inflammatory cells, granulation tissue, fibrosis, and new bone formation. Each horizontal section of the cochlea containing the modiolus was assessed. We also analyzed the cochlear area (for both bony and lumen areas) in the basal turn of all horizontal sections containing the round window (Figure 1).



**FIGURE 1** Horizontal section of a right temporal bone from a patient in the control group to represent how the area of the basal turn was obtained

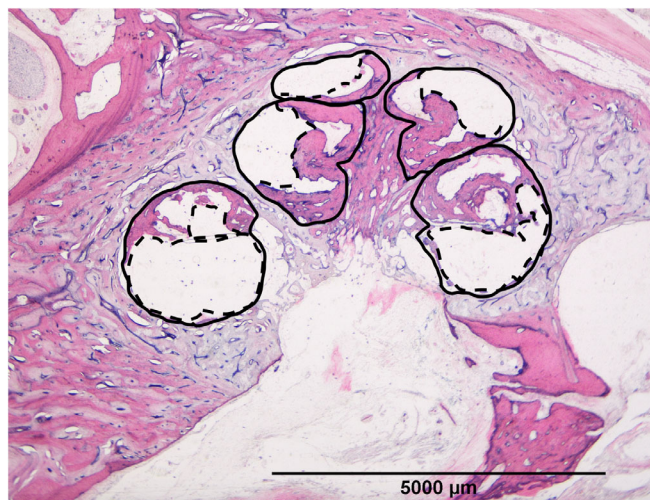


**FIGURE 3** This is a mid-modiolar section from a right temporal bone from a patient included in the meningitis group. Note the presence of fibrous tissue and new bone formation within the cochlear turns. (\*) labyrinthitis ossificans within the *scala vestibuli* of the cochlea; (+) labyrinthitis ossificans within the *scala tympani* of the cochlea



**FIGURE 2** Example of how measurements were obtained. A, limits of cochlear lumen; B, limits of bony cochlear turns

Each cochlear turn was evaluated using two measurements: (a) the bony borders of the cochlear fluid spaces, and (b) the area of its lumen. If new bone formation or fibrous tissue were present and resulted in a labyrinthitis ossificans that obliterated the entire cochlear turn, we considered the lumen as absent. However, if any lumen was



**FIGURE 4** Midmodiolar section of a right cochlea from a patient with hearing loss following meningitis. Dashed line = limits of cochlear lumen; solid line = limits of bony cochlear turns

seen, we measured it (Figures 2 and 3). The area for each cochlear turn, in the horizontal sections containing the modiolus, was measured and averaged to compare the different groups (Figure 4).

The measurement of the area of the cochlea in the temporal bone sections was performed using a camera attached to an optical microscope under  $\times 20$  magnification, then transferred the images to a personal computer for measurements. Next, we measured the area of the cochlea in each specific turn. To evaluate the cochlear system under light microscopy, we used a 64-bit Nikon Eclipse E400 imaging system equipped with measurement software (NIS-Elements Basic Research, version 4.30.01, Nikon, Instruments Inc., Tokyo, Japan).

To quantify the severity of fibrous tissue or labyrinthitis ossificans, the area of membranous labyrinth replaced by inflammatory cells (ie, lymphocytes, macrophages, or monocytes) or new bone formation was measured using ImageJ software (version 1.52k, NIH).

To evaluate the effect of meningitis to the cochlea, the *meningitis group* was divided into two different subgroups, taken the time course from the diagnosis of meningitis to the death of each patient. The first subgroup was consisted of patients who had meningitis within 30 days of death (meningitis and/or its complications was considered as the cause of death). The second subgroup was consisted of patients who had meningitis for a longer period than 30 days of death (patients had meningitis, survived, and died for other reasons). Then, the results were compared among the *control group*. The results were expressed as mean area per cochlear turn, and per cochlear lumen, in  $\mu\text{m}^2$ .

**TABLE 1** Clinical data from patients with meningitis

Case	Side	Age of death	Sex	Etiologic agent	Time from meningitis to death
1	Left	13 y	Female	<i>Streptococcus pneumoniae</i>	10.5 y
2	Right	13 y	Female	<i>Streptococcus pneumoniae</i>	10.5 y
3	Left	4 y	Female	<i>Neisseria meningitidis</i>	9 d
4	Right	4 y	Female	<i>Neisseria meningitidis</i>	9 d
5	Left	72 y	Male	<i>Haemophilus influenzae</i> type B	52 y
6	Right	5 y	Male	<i>Streptococcus pneumoniae</i>	3.5 y
7	Left	78 y	Female	?	23 y
8	Left	49 y	Male	<i>Haemophilus influenzae</i> type B	49 y
9	Right	49 y	Male	<i>Haemophilus influenzae</i> type B	49 y
10	Right	3 mo	Male	<i>Neisseria meningitidis</i>	3 d
11	Left	3 mo	Female	?	4 d
12	Right	1.5 y	Male	<i>Streptococcus pneumoniae</i>	1.5 y
13	Left	84 y	Male	?	83 y
14	Right	84 y	Male	?	83 y
15	Left	56 y	Female	<i>Neisseria meningitidis</i>	52 y
16	Right	56 y	Female	<i>Neisseria meningitidis</i>	52 y
17	Left	60 y	Male	<i>Streptococcus pneumoniae</i>	30 d
18	Right	60 y	Male	<i>Streptococcus pneumoniae</i>	30 d
19	Left	80 y	Female	<i>Haemophilus influenzae</i> type B	79.5 y
20	Left	4 y	Female	<i>Neisseria meningitidis</i>	3 d
21	Right	4 y	Female	<i>Neisseria meningitidis</i>	3 d
22	Right	41 y	Male	<i>Streptococcus pneumoniae</i>	10 d

## 2.3 | Ethics

The Institutional Review Board of the University of Minnesota (0206M26181) and the Ethics in Research Committee of the Clinical Hospital of the Ribeirão Preto Medical School—University of São Paulo (CEP 2.099.454) approved this study.

## 2.4 | Statistical analysis

Results are presented as the mean  $\pm$  SD. The two groups were compared together using the Mann-Whitney *U* test. The comparison of the variables between the two groups was used to calculate the sample size, setting the level of significance at 5% (*alpha* or type I error) and the power of the sample at 80% (*beta* or type II error of 20%). Findings were considered statistically significant when *P* values were less than .05. The SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis.

## 3 | RESULTS

The selected temporal bones were age- and sex-matched, as closely as possible. Our final *meningitis group* included a total of 22 temporal bones, from 15 patients with a clinical diagnosis of meningitis (history of fever, altered mental status, neck stiffness, cerebrospinal fluid (CSF—culture positive, polymorphonuclear pleocytosis, hypoglycorrhachia), and raised CSF protein levels; Table 1). This consisted of 8 males and 7 females; aged  $38.65 \pm 32.24$  years (range: 0.25–84 years).

The *meningitis group* was divided into two subgroups: the first was consisted of nine patients who had meningitis and died within 30 days of the infection, and the second subgroup was consisted of 13 patients who had a history of meningitis but died after 30 days of the disease.

Our *control group* included 22 temporal bones from 11 donors with no history of meningitis and no histologic signs of middle ear or inner ear diseases; they were 6 males and 5 females; mean age  $38.27 \pm 23.29$  years (range: 10–82 years).

**TABLE 2** Mean bony area of cochlear turns in midmodiolar section in *meningitis group* and the *control group* (results are presented as mean  $\pm$  SD, area as  $\mu\text{m}^2$ )

	Meningitis		Control
	<30 d	>30 d	
Turn 1	$3.6 \pm 0.67^a$	$2.91 \pm 0.34^b$	$3.35 \pm 0.32$
Turn 2	$3.5 \pm 0.42^a$	$2.64 \pm 0.33^b$	$3.32 \pm 0.36$
Turn 3	$2.28 \pm 0.29$	$2.2 \pm 0.45$	$2.36 \pm 0.17$
Turn 4	$2.56 \pm 0.84$	$2.04 \pm 0.34^b$	$2.98 \pm 0.91$
Turn 5	$1.46 \pm 0.14$	$1.46 \pm 0.47$	$1.74 \pm 0.58$

<sup>a</sup>Statistically significant, as compared within the *meningitis group*.

<sup>b</sup>Statistically significant, as compared to the *control group*.

## 3.1 | Assessment of the presence and location of inflammatory cells

We observed the presence of few to abundant inflammatory cells (eg, macrophages, lymphocytes, or monocytes) in the cochlea among 14 temporal bones (63.64%). The inflammatory cells were found mostly in the scala tympani among these 14 temporal bones. Of the 22 temporal bones in the *meningitis group*, 9 (40.9%) presented inflammatory cells and new bone formation at the level of the round window (in 4 cases [18.18%], total blockage of the round window was seen) next to the entrance of the cochlear aqueduct.

## 3.2 | Cochlear area

The mean area of the bony walls of all cochlear turns is reduced within the *meningitis group*, and it was significantly reduced in turns 2 and 4 ( $P < .05$ , Table 2).

The mean area of the lumen of all cochlear turns is reduced within the *meningitis group*. The reduced lumen was mainly because of the presence of inflammatory cells and fibrous tissue. However, we also observed the presence of new bone formation within the cochlear lumen. The lumen was significantly reduced in all turns but turn 5 ( $P = .3749$ , Table 3).

We also observed a significant decrease in basal turn areas among patients in the *meningitis group* (Table 4).

**TABLE 3** Mean lumen area of cochlear turns in midmodiolar section in *meningitis group* and the *control group* (results are presented as mean  $\pm$  SD, area as  $\mu\text{m}^2$ )

	Meningitis		Control
	<30 d	>30 d	
Turn 1	$2.98 \pm 0.65^a$	$1.92 \pm 0.8^b$	$2.74 \pm 0.31$
Turn 2	$2.97 \pm 0.41^a$	$1.85 \pm 0.66^b$	$2.75 \pm 0.31$
Turn 3	$1.93 \pm 0.26^a$	$1.55 \pm 0.48^b$	$2.00 \pm 0.17$
Turn 4	$2.28 \pm 0.81^a$	$1.7 \pm 0.48^b$	$2.64 \pm 0.86$
Turn 5	$1.28 \pm 0.11$	$1.2 \pm 0.46$	$1.54 \pm 0.56$

<sup>a</sup>Statistically significant, as compared within the *meningitis group*.

<sup>b</sup>Statistically significant, as compared to the *control group*.

**TABLE 4** Mean area of basal turn in horizontal sections in *meningitis group* and the *control group* (results are presented as mean  $\pm$  SD, area as  $\mu\text{m}^2$ )

	Bony area	Lumen area
Meningitis		
<30 d	$14.99 \pm 1.26^a$	$10.26 \pm 1.38^{a,b}$
>30 d	$13.76 \pm 1.73^a$	$8.11 \pm 1.89^a$
Control	$15.92 \pm 0.76$	$13.41 \pm 0.62$

<sup>a</sup>Statistically significant, as compared to the *control group*.

<sup>b</sup>Statistically significant, as compared within the *meningitis group*.

## 4 | DISCUSSION

As demonstrated in this present study, the area of the bony wall in the cochlear turns, as well as the cochlear lumen, among patients with a history of meningitis is reduced when compared to a nondiseased control group.

As a result of labyrinthitis ossificans and massive damage in the inner ear structures, hearing loss is a frequent sequela of meningitis.<sup>5</sup> Cochlear implantation is the treatment of choice in profound deafened patients after meningitis and pre-operatively imaging must be performed.<sup>5-7</sup>

Residual hearing preservation after conventional cochlear implant surgery was observed in patients with larger cochlear volume and longer cochlear duct length, as demonstrated by Takahashi et al.<sup>6</sup> They observed that both measurements were significantly larger among patients with complete hearing preservation. However, they excluded patients with structural cochlear malformations, such as Mondini, or intracochlear ossification.

The present study performed cochlear area measurements using histological sections of human temporal bones which is believed to be more accurate than those of radiologic studies. Isaacson et al<sup>8</sup> found the sensitivity and specificity of magnetic resonance imaging to assess intraoperative cochlear obstruction to be 94.1% and 87.5%, respectively. They recommend radiographic monitoring or early cochlear implantation since labyrinthitis ossificans may occur as early as 2 weeks after bacterial meningitis. Liu et al<sup>9</sup> demonstrated that pediatric patients with no labyrinthitis ossificans (ie, larger residual cochlear volume) presented better speech perception category outcomes after cochlear implantation than those with cochlear ossification following bacterial meningitis. It is expected that larger residual cochlear volume affects residual hearing preservation after cochlear implantation because the full electrode insertion in the scala tympani can be achieved.

Meningitis may cause deafness in up to 10% of cases, and around one-third of them, the cochlea may be found obliterated.<sup>5</sup> Those findings show that in cases of profound hearing loss following meningitis, patients should be promptly referred for cochlear implantation before significant cochlear ossification occurs. However, the audiologic outcomes are difficult to predict, particularly in the presence of cochlear ossification.<sup>6</sup> Furthermore, it was demonstrated that meningitis leads to multifocal lesions (acute inflammatory, toxic or ischemic damage) to central nervous system pathways, as well as to the labyrinth.<sup>6</sup>

Despite these observations, it was demonstrated that patients may also benefit from partial insertion of a cochlear implant.<sup>5</sup> Therefore, we can expect that even smaller cochlear volumes may reach proper audiologic outcomes after cochlear implantation.

This study has several limitations. Although we described specific histopathologic findings, the results cannot be generalized to all meningitic labyrinthitis—further analysis of cases with otogenic labyrinthitis leading to meningitis may be required. Our sample was relatively small. The clinical history of each subject may have been incompletely reported. Furthermore, none of the subjects had documented audiological or radiological evaluations.

In summary, we observed a reduced area in the mid-modiolar sections and basal turn sections at the level of the round window among

patients with a history of meningitis. Future studies may better correlate audiologic outcomes, cochlear volume, and cochlear area among patients with meningitis.

## 5 | CONCLUSION

The analysis of the cochlear turns area among patients with a history of meningitis demonstrated distinct reduction as compared to a non-diseased control group. Future studies are necessary to determine whether these findings are related to volumetric cochlear changes and audiologic outcomes.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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