Histopathologic Features of the Temporal Bone in Patients With Cystic Fibrosis

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**Objectives:** To investigate the lower than expected incidence of otitis media in patients with cystic fibrosis (CF) through histopathologic evaluation of temporal bones and to document pathologic findings in the inner ears of patients with CF who received long-term administration of antibacterial and diuretic agents.

**Design:** Clinical records of patients who died of CF were reviewed. Their temporal bones were sectioned, stained with hematoxylin-eosin, and examined histologically. Additional sections were stained with Alcian blue and periodic acid-Schiff for comparison of goblet cell densities from middle ears and auditory tubes of patients with CF with those of control temporal bones. Results were analyzed using the t test.

**Subjects:** Twenty-one temporal bones from 11 patients with CF and 13 bones from 8 age-matched patients without CF were selected.

**Results:** All temporal bones with CF had well-pneumatized mastoids. Temporal bones from 2 patients (3 ears) revealed histological findings of chronic otitis media with effusion. There was a statistically significant reduction in the density of goblet cells in the medial (P = .002) and lateral (P = .05) walls in patients with CF who had no otitis media histologically compared with control temporal bones. Two patients with CF who had otitis media had increased densities of goblet cells. Inner ear damage, due to ototoxic drugs, was seen in most of the temporal bones from patients with CF.

**Conclusion:** Low densities of goblet cells in temporal bones with CF may contribute reduced amounts of viscous mucus, which can lead to a low incidence of otitis media.

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Cystic fibrosis (CF) is an autosomal recessive and life-limiting genetic disease commonly seen among white children (1 in 1000-4000 live births). The disease affects the exocrine glands, eventually putting the organs housing this type of gland in a nonfunctioning state. The main clinical manifestations of CF in the upper respiratory tract system are sinusitis, rhinitis, and nasal polyposis. Because the auditory tube and the middle ear are expanded portions of the upper respiratory tract system, several investigators have studied possible involvement of the middle ear in patients with CF.

Kulczycki and colleagues noted hearing loss in only 8% of their patients with CF, and Jorissen et al described a series showing pathologic conditions in the middle ears of half of their patients with CF. Most investigators have reported no substantial differences in the incidence of middle ear infections between populations with and without CF. Although these results seem to conflict, partly because of differences in their patient populations, locations, and methods, the incidence of infections in the middle ear in patients with CF is believed to be lower than expected. This unexpectedly lower incidence is puzzling because conditions in patients with CF, such as sinusitis, allergies, nasal polyposis, and other complications of the upper respiratory tract system, are well-known as factors predisposing to otitis media.

This study examines the temporal bones of patients with CF for any histopathologic findings in the middle ear that might explain the lower incidence of otitis media. We also studied the pathologic conditions of the inner ear resulting from long-term administration of ototoxic substances—gentamicin sulfate, tobramycin sulfate, amikacin sulfate, vancomycin hydrochloride, and furosemide—commonly used in the treatment of CF.

**Results**

The examination results of 21 temporal bones with CF revealed slight fibrous thickening in the tympanic mucosa, a few fibrous bands in the tympanic cavity, and serous fluid in some of the mastoid air cells in 2 specimens. A few free leukocytes and erythrocytes were seen in the mastoid and the middle ear space in another specimen, and a small amount of serous secretion was seen in 4 specimens. Both temporal bones...
of 1 patient showed severe chronic otitis media with effusion, and 1 specimen of another patient had moderate thickening of the mucosa of the middle ear. (We excluded these temporal bones from analysis of goblet cell densities.) Thus, our study showed the histopathologic evidence of otitis media in 3 (14%) of the 21 ears. The mastoids were well pneumatized in all temporal bones. The examination results of slides stained with periodic acid–Schiff and Alcian blue from 18 temporal bones revealed statistically significant differences in numbers of goblet cells between temporal bones from patients with CF without evidence of otitis media and those from controls (Table 1 and Figure 1).

Table 1. Density of Goblet Cells in the Middle Ear and the Auditory Tube*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medial Wall</th>
<th>Lateral Wall</th>
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<tbody>
<tr>
<td>Patients (n = 18)</td>
<td>44.62 ± 58.29</td>
<td>129.87 ± 145.92</td>
</tr>
<tr>
<td>Controls (n = 13)</td>
<td>220.33 ± 154.89</td>
<td>255.31 ± 179.08</td>
</tr>
</tbody>
</table>

*Data are given as the mean ± SD. The differences between patients and controls were statistically significant for the medial wall (P = .002) and the lateral wall (P = .05).

Audiogram results were available for 5 patients. Two showed normal hearing, 1 showed low-frequency sensorineural hearing loss, and 2 showed high-frequency sensorineural hearing loss (Figure 2, top). The evaluation of hair cells was not done in 6 temporal bones (from patients 3, 6, and 9) because of compression artifact in the spiral organ. All other temporal bones, with the exception of patient 1, revealed varying degrees of histopathologic findings in the inner ear (Table 2 and Figure 2, bottom). Pathologic conditions of the upper respiratory tract noted in clinical histories included sinusitis, rhinitis, nasal polyps, allergy, and otitis media (Table 3).

**COMMENT**

Because there is a higher incidence of complications of the upper respiratory tract (sinusitis, allergies, rhinitis, and nasal polyps) in patients with CF, a higher incidence of otitis media might be expected as well. Although earlier studies described a higher incidence of hearing problems related to the middle ear in patients with CF compared with normal populations, most recent studies including a prospective study, support a low prevalence of diseases of the middle ear in these patients. Bak-Pedersen and Larsen found histories of otitis media in 35% of the patients with CF in their retrospective study, and Jorissen
and colleagues\textsuperscript{5} found a positive history of otitis media in 33% of the patients with CF in a prospective study. These ratios are consistent with the findings of a 37.5% incidence of otitis media in the general population of children.\textsuperscript{12} In our series, we found histopathologic evidence of otitis media with effusion in 3 (14%) of the 21 ears. This prevalence of 14% is completely within the expected range for a control population and similar to the finding (11%) reported by otoscopic and tympanometric examinations by Jorissen and coworkers.\textsuperscript{5} Similar results have also been reported by Haddad et al.\textsuperscript{10}

The lower than expected incidence of otitis media in patients with CF has been suggested to be due to the long-term administration of antibiotics for the treatment of respiratory tract infection.\textsuperscript{3,11} In our series, patients were treated with long-term antibiotics but had a high incidence of sinusitis and a lower than expected incidence of otitis media, similar to the findings by Cuyler and Monaghan.\textsuperscript{2} Although the use of ototoxic drugs resulted in damage to the inner ears of most of the temporal bones we studied, the idea that such drugs could prevent otitis media but not sinusitis seems unlikely.

Ozcelik et al\textsuperscript{11} investigated the hearing status of children with CF by complete audiometric evaluation and brainstem-evoked response audiometry and found that CF did not affect hearing. Although audiometric evaluation was only available for a few of our patients, we observed histopathologic findings in the inner ears of all of them. We believe that ototoxic drugs, although essential for the prevention of life-threatening infections in patients with CF, should be used with caution.

An interesting finding in our study is that all patients with CF, even patients with otitis media, had well-pneumatized mastoids, and similar findings have been demonstrated on computed tomographic scans by Todd and Martin.\textsuperscript{13} Sade and Fuchs\textsuperscript{14,15} found that patients with
mastoid pneumatization less than 6 cm² were 18 times more prone to acquire otitis media with effusion than those with better pneumatization. Furthermore, it is well-known that long-standing ear infections halt the development of pneumatization in mastoids. Well-pneumatized mastoids found in patients with CF may suggest a decreased incidence of chronic ear infection.

A probable explanation for the low incidence of otitis media in patients with CF is the lower densities of goblet cells in the mucosa of the middle ear and the auditory tube of patients with CF compared with controls (temporal bones without CF). The smaller number of goblet cells and mucous glands in the auditory tube and middle ear cavity in patients with CF has been speculated to be a cause of their low incidence of otitis media. Our findings of lower densities of goblet cells in the mucosa of the middle ear and auditory tube of patients with CF vs the middle ear mucosa and auditory tube of a normal population may provide a logical basis for the low prevalence of ear disease in patients with CF.

Dysfunction of the mucociliary clearance system may be another mechanism in the pathogenesis of otitis media. Takasaka and Kawamato have demonstrated that primary mucociliary dysfunction would cause dysfunctional clearance of the auditory tube and result in effusions in the middle ear. However, in a study of mucociliary clearance in patients with CF, Kollberg and coworkers have suggested that impairment of mucociliary clearance would not be a primary pathogenic factor for respiratory tract disease in patients with CF.

Another possible explanation for the low incidence of otitis media in these patients with CF may be related to their expression of mucin genes. To date, several human mucin sequences have been classified, showing their expression to be organ specific. Although there have been numerous studies of gene expression of mucus in the airways and gastric system, there is little information on gene expression for mucus in the middle ear. It may be that differences between gene expression for mucus in the epithelium of the upper respiratory tract and in the epithelium of the middle ear explain the discrepancy from the expected prevalence of otitis media in patients with CF.

### Table 3. Otolaryngological Findings of 11 Patients With Cystic Fibrosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sinusitis</th>
<th>Rhinitis</th>
<th>Nasal Polyps</th>
<th>Nasal Allergy</th>
<th>History of Otitis Media</th>
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<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<tr>
<td>2</td>
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<tr>
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<td>11</td>
<td>+</td>
<td>+</td>
<td>–</td>
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</table>

Total, No. (%) 11 (100) 7 (63.6) 3 (27.3) 3 (27.3)

* Plus sign indicates the presence of the finding; minus sign, the absence of the finding.

### REFERENCES