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Changes in the inner ear structures in cystic fibrosis patients

Henrique F. Pauna [a, b], Rafael C. Monsanto [a, c], Natsuko Kurata [a, d], Michael M. Paparella [a, e], Sebahattin Cureoglu [a, *]

[a] Department of Otolaryngology, Head & Neck Surgery, University of Minnesota Minneapolis, MN, USA
[b] Department of Otolaryngology, Head and Neck Surgery, State University of Campinas/UNICAMP, Campinas, São Paulo, Brazil
[c] Department of Otolaryngology and Head and Neck Surgery, Banco de Olhos de Sorocaba Hospital (BOS), Sorocaba, São Paulo, Brazil
[d] Tokyo Medical and Dental University, Tokyo, Japan
[e] Paparella Ear Head & Neck Institute, Minneapolis, MN, USA

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ABSTRACT

Objective: Although prolonged use of antibiotics is very common in cystic fibrosis (CF) patients, no studies have assessed the changes in both cochlear and peripheral vestibular systems in this population.
Methods: We used human temporal bones to analyze the density of vestibular dark, transitional, and hair cells in specimens from CF patients who were exposed to several types of antibiotics, as compared with specimens from an age-matched control group with no history of ear disease or antibiotic use. Additionally, we analyzed the changes in the elements of the cochlea (hair cells, spiral ganglion neurons, and the area of the stria vascularis). Data was gathered using differential interference contrast microscopy and light microscopy.
Results: In the CF group, 83% of patients were exposed to some ototoxic drugs, such as aminoglycosides. As compared with the control group, the density of both type I and type II vestibular hair cells was significantly lower in all structures analyzed; the number of dark cells was significantly lower in the lateral and posterior semicircular canals. We noted a trend toward a lower number of both inner and outer cochlear hair cells at all turns of the cochlea. The number of spiral ganglion neurons in Rosenthal's canal at the apical turn of the cochlea was significantly lower; furthermore, the area of the stria vascularis at the apical turn of the cochlea was significantly smaller.
Conclusions: Deterioration of cochlear and vestibular structures in CF patients might be related to their exposure to ototoxic antibiotics. Well-designed case-control studies are necessary to rule out the effect of CF itself.

1. Introduction

Cystic fibrosis (CF), an autosomal recessive hereditary disease, is common among the white population. It primarily affects exocrine gland function and the viscosity of mucous secretion. Overall, the median survival time for CF patients is around 30 years, but children born in the United States in 1990 are projected to live longer than 40 years [1]. In 1989, the CF transmembrane conductance regulator (CFTR) gene was identified in the long arm of chromosome 7; its mutations can result in abnormal chloride ion transport [1–3].

CF patients are often repeatedly treated with a long-term course of antibiotics. Given the known accumulation of toxic antibiotics in other organs after prolonged antibiotic treatment, it is likely that the perilymph of the inner ear (including the cochlea and vestibule) is also affected [4]. Yet, in CF patients, an untreated infection due to *Pseudomonas aeruginosa* can result in progressive lung damage (bronchiectasis), respiratory failure, and death [4,5].

Despite the higher incidence of respiratory infections in CF patients, their incidence of otitis media in this population remains under debate; in fact, studies published in this regard show conflicting data [1,6,7]. Although hearing impairment is easily recognizable in these patients, the vestibular symptoms due to damage in the vestibular system are insidious and include vague dizziness, vertigo, or a light-headed sensation, constituting a diagnostic challenge to both pediatricians and otolaryngologists [5]. Only a few studies have included histologic evaluation of the vestibular

Abbreviations: CF, cystic fibrosis.

* Corresponding author. Department of Otolaryngology, University of Minnesota, Lions Research Building, Room 210, Mayo Mail Code 2873, 2001 6th Street SE, Minneapolis, MN 55455, USA.
E-mail address: cureo003@umn.edu (S. Cureoglu).

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end organs in patients exposed to ototoxic antibiotics [8,9].

To the best of our knowledge, ours is the first study to analyze the changes in both inner ear structures (cochlea and vestibule) of CF patients exposed to a several types of antibiotics, as compared with a control group of patients with no history of ear disease or antibiotic use, looking for initial changes that may indicate clinical features of the patients.

2. Materials and methods

From our archived human temporal bone collection at the University of Minnesota, we selected specimens for this study from deceased donors with a clinical diagnosis of CF by positive sweat test (sweat chloride value above 60 mEq/L [1,10]). Excluded were specimens from donors who had tumors affecting the ear; who had leukemia; who underwent irradiation of the head and neck, chemotherapy, or any otologic surgery; who had clinical otosclerosis or a systemic autoimmune disease; or whose temporal bones were affected by processing artifacts. The final *CF group* (Table 1) included 12 specimens (from 5 males and 7 females); their mean age was 23.0 ± 11.88 years (range, 10–49 years). All 12 of them had a history of antibiotic use.

Our age-matched *control group* included 12 specimens from donors with no history of ear disease or antibiotic use; their mean age was 29.27 ± 14.87 years (range, 3–69 years).

Using light microscopy, 3 of the authors (HFP, RCM, NK) independently scrutinized the slides of the specimens; the authors were blinded to information such as the age, gender, or medical history of the temporal bone donor. Then, the results obtained by the 3 authors were compared and reevaluated by a 4th author (SG).

The specimens 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.

2.1. Vestibular hair cells

To measure hair cell density, we scrutinized every 10th horizontal section of the maculae of the saccule and utricle, as well as of the cupulae of the lateral and posterior semicircular canals. Excluded from our analysis were the structures in the anterior semicircular canal: they are usually absent because of our processing routine, which involves horizontally cutting the temporal bones.

We distinguished vestibular hair cells on the basis of their morphologic features: type I cells have a round nerve chalice (giving these cells a piriform shape) and a spherical nucleus; type II

Table 1
Epidemiologic characteristics of our CF group.

Donor no.	Age, y/Gender/Race	Family history of CF	Ear infection	Symptoms	Antibiotics used	Culture results
1[a]	7/M/white	NA	No	No	tetracycline	NA
2	11/M/white	NA	No	NA	dicloxacillin, sulfisoxazole, erythromycin, polymyxin, gentamicin, carbenicillin	NA
3	18/F/white	No	No	No	sulfamethoxazole, ampicillin, sulfamethoxazole and trimethoprim, gentamicin	*Pseudomonas aeruginosa, Staphylococcus aureus*
4[a]	40/M/white	Yes	No	Tinnitus	doxycycline, tobramycin, ticarcillin, piperacillin, ampicillin, amikacin, ciprofloxacin	*Pseudomonas aeruginosa*
5[a]	21/F/white	NA	No	Dizziness (ENG normal but with hypofunction bilaterally)	tobramycin, piperacillin, sulfamethoxazole and trimethoprim, ceftazidime, vancomycin, chloramphenicol	*Pseudomonas cepacia*
6[a]	27/F/white	NA	No	Vertigo and tinnitus (ABR normal bilaterally, ENG with no function)	ceftizoxime, doxycycline, trimethroprim, nafcillin, tobramycin, ticarcillin, amoxicillin	*Pseudomonas cepacia, Pseudomonas aeruginosa, Serratia marcescens, Haemophilus influenzae, Aspergillus fumigatus*
7[a]	25/F/white	NA	No	NA	doxycycline, chloramphenicol, imipenem, tobramycin, sulfamethoxazole, clindamycin	*Pseudomonas aeruginosa, Candida*
8	20/F/white	NA	No	NA	tobramycin, imipenem, piperacillin, ciprofloxacin, aztreonam, Timentin, ceftazidime, tetracycline, Adriamycin	*Pseudomonas aeruginosa*
9	11/F/white	NA	NA	NA	ticarcillin, tobramycin, vancomycin, amphotericin B, itraconazole	*Pseudomonas aeruginosa, Streptococcus, Micrococcus, Aspergillus*
10	16/F/white	NA	No	No	tobramycin, ciprofloxacin, imipenem, fluconazole, chloramphenicol	*Pseudomonas aeruginosa, Aspergillus fumigatus*
11	28/M/white	NA	No	No	imipenem-tobramycin, Timetin-tobramycin, erythromycin, ciprofloxacin, ceftizoxime, aztreonam	*Pseudomonas aeruginosa*
12	49/M/white	NA	No	No	sulfamethoxazole and trimethoprim, itraconazole, Timentin	*Aspergillus fumigatus, Stenotrophomonas maltophilia*

ABR = auditory brain response; CF = cystic fibrosis; ENG = electronystagmography; F = female; M = male; NA = not available; No. = number; y = years.
[a] Audiogram information available.