



the Registry

Contents

SCIENTIFIC ARTICLE:

Selective Inner Hair Cell Loss in Premature Infants.....1

REGISTRY AND OTHER NEWS:

Otopathology Mini-Travel Fellowship.....5

Upcoming meetings.....5

Order form for Temporal Bone Donation Brochures.....6

Mission Statement

The NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry was established in 1992 by the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health to continue and expand upon the former National Temporal Bone Banks (NTBB) Program. The Registry promotes research on hearing and balance disorders and serves as a resource for the public and the scientific community about research on the pathology of the human auditory and vestibular systems.

Selective Inner Hair Cell Loss in Premature Infants

Monica Amatuzzi¹, M. Charles Liberman^{2,3} and Clarinda Northrop^{2,4}

¹ Dept. of Otorhinolaryngology, Universidade de São Paulo, Brazil

² Dept. of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, USA

³ Dept. of Otolaryngology and Laryngology, Harvard Medical School, Boston, MA, USA

⁴ Temporal Bone Foundation, Boston, MA, USA

Introduction

Infants from the neonatal intensive care unit (NICU) often have sensorineural hearing loss. Many risk factors have been suggested including low birth weight, respiratory distress, hyperbilirubinemia, acoustic injury and ototoxic drugs; however, little is known about the underlying cochlear histopathology.

In a prior study of temporal bones from 15 NICU patients, selective inner hair cell loss was seen in three cases (1). The finding was surprising since selective inner hair cell loss is an uncommon pathology in both the human (4,5) and animal literature (2,3,7). The finding was also intriguing, because all three cases were preterm babies.

We conducted a study of 100 temporal bones in order to better understand the frequency of selective inner hair cell loss in infants, and its relation to gestational age.

Material and Methods

We studied temporal bones of all the preterm neonates from the Temporal Bone Foundation Collection, i.e. 27 cases (54 ears) consisting of 17 male and 10 female patients, born between 26 and 36 weeks gestation. The age at time of death varied from 1 day to 6 months, and the birth weight ranged from 800g to 2800g. The control group included 23 neonates (46 ears) from the collection, age-matched to the first group. They were 14 males and 9 females, 37 to

Directors:

Joseph B. Nadol, Jr., M.D.
Saumil N. Merchant, M.D.
Steven D. Rauch, M.D.
Michael J. McKenna, M.D.
Joe C. Adams, Ph.D.

Scientific Advisory Council:

Newton J. Coker, M.D.
Howard W. Francis, M.D.
Marlan R. Hansen, M.D.
Raul Hinojosa, M.D.
Akira Ishiyama, M.D.
Herman A. Jenkins, M.D.
Elizabeth M. Keithley, Ph.D.
Robert I. Kohut, M.D.
Fred H. Linthicum, Jr., M.D.
Saumil N. Merchant, M.D.
Joseph B. Nadol, Jr., M.D.
Michael Paparella, M.D.
Jai H. Ryu, Ph.D.
Isamu Sando, M.D., D.M.Sc.
P. Ashley Wackym, M.D.
Charles G. Wright, Ph.D.

Coordinator:

Nicole Pelletier

Administrative Staff:

Kristen Kirk-Paladino
Tammi N. King
Jon Pack

Newsletter Editors:

General: Suzanne Day
Medical: Saumil N. Merchant, M.D.

NIDCD National Temporal Bone, Hearing
and Balance Pathology Resource Registry

Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114

(800) 822-1327 Toll-Free Voice
(617) 573-3711 Voice
(617) 573-3838 Fax

Email: tbregistry@meei.harvard.edu

Web: www.tbregistry.org

43 weeks gestation, with birth weights from 2250g to 4800g, and aged from 1 day to 8 months at time of death. All temporal bones had been collected from the NICU at the Hospital de Ninios in San Jose, Costa Rica between 1977 and 1993.

Temporal bones were fixed 1 to 15 hrs after death in neutral-buffered (10%) formalin, decalcified with 5% trichloroacetic acid, and embedded in celloidin. The blocks were cut at 20 μ m in the horizontal plane, and every 10th section was stained with hematoxylin-eosin. Every stained section from all 100 temporal bones was analyzed using high-power oil immersion objectives. Tissue preservation allowed identification of inner hair cells (IHC) and outer hair cells (OHC) based on the combined presence or absence of nuclei, cuticular plates and hair bundles (Figure 1). To

eliminate post-mortem autolysis, we only considered hair cell loss in which the reticular lamina had re-sealed to fill the gap, suggesting that the damage was more than 1-2 days old. Guild's 2-dimensional technique was used to reconstruct the cochlear spiral in all cases, and the organ of Corti was evaluated in each section (4). The loss of inner and outer hair cells was quantified, and the condition of the supporting cells, stria vascularis, spiral ligament, Reissner's membrane and the spiral ganglion were qualitatively evaluated in each section.

Results

Qualitative analysis:

Within the organ of Corti, significant loss of hair cells was commonly seen in both full-term and preterm infants. In the full-term infants, that loss was

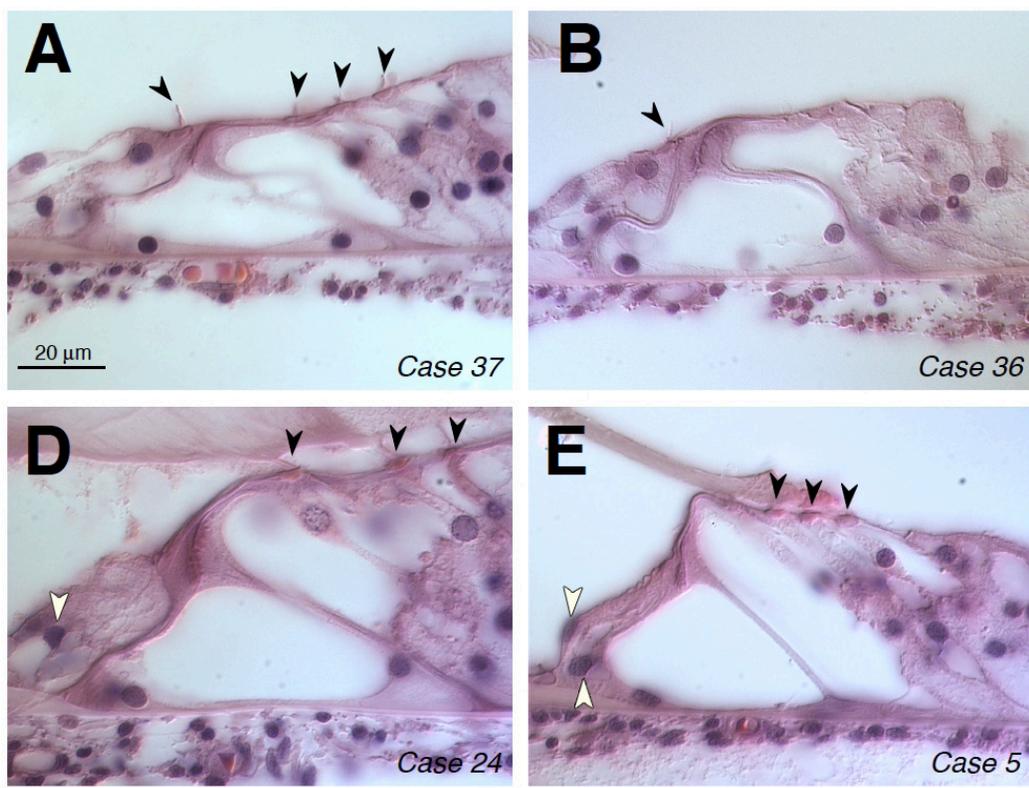


Figure 1.

Tissue preservation was adequate in most cases to allow identification of inner and outer hair cells based on the combined presence or absence of nuclei, cuticular plates, and hair bundles. Filled arrowheads point to remaining hair bundles and cuticular plates; open arrowheads point to nuclei of remaining supporting cells in the IHC area. Note that the reticular lamina is intact in regions of hair cell loss.

typically seen as selective loss of outer hair cells (e.g., Figure 1B) or combined loss of inner and outer hair cells (e.g., Figure 1C). In the preterm cases (e.g. Figure 1D–F), there was a surprising number of cases with selective loss of inner hair cells: ten ears from five infants. When selective inner hair cell loss was seen, the supporting cells in the IHC area appeared to be intact (Figure 1D–F), and both inner and outer pillar cells appeared normal and present in normal numbers.

Qualitative analysis of the spiral ganglion suggested no loss of neurons, even in the cases of widespread IHC loss. There was little clearcut pathology in any of the accessory structures of the cochlear duct, i.e., stria vascularis, spiral ligament, spiral limbus, and Reissner's or tectorial membranes.

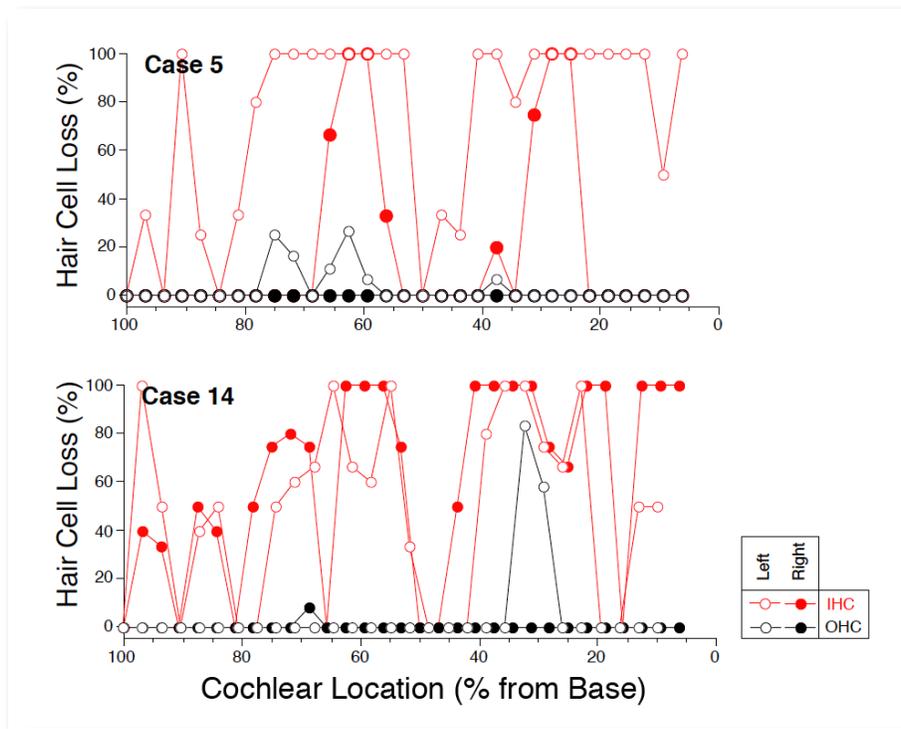


Figure 2. Two examples of selective IHC loss in preterm cases. There was widespread loss of IHCs in all turns of the cochlea (red symbols) with minimal OHC loss (black symbols).

Hair cell counts:

Of the preterm and full-term ears that passed the postmortem autolysis screen, 22 of 37 (59%) and 26 of 36 (72%), respectively, were classified as normal, i.e., showing no more than two consecutive slides with any hair cell loss in any of the four rows. Selective loss of OHCs was seen in 4 of 37 (11%) of preterm and 6 of 36 (17%) of full-term ears. This condition was typically bilateral. The cytochleograms showed that selective OHC loss was usually present in the basal half of the cochlea.

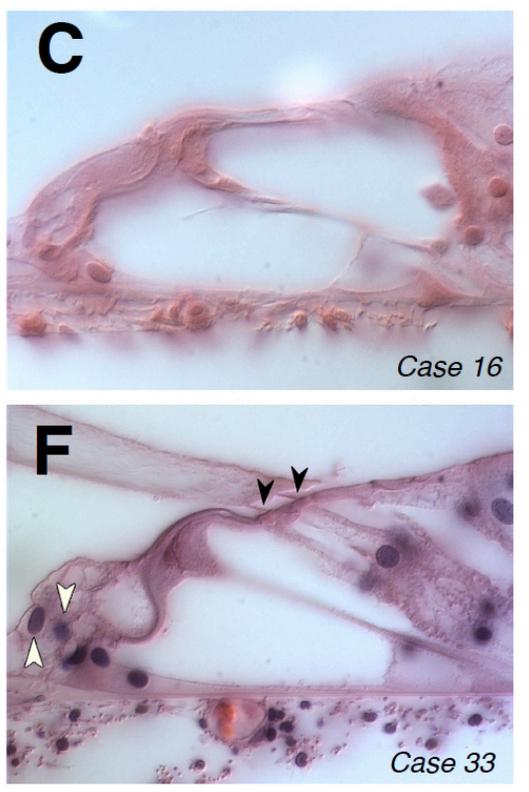
Combined and co-extensive loss of IHCs and OHCs was seen in 1 of 37 pre-term ears and 3 of 36 full-term ears. The damage was seen throughout the cochlear spiral in many of these cases. In only one ear was the damage restricted to a relatively small island in the basal turn.

Large regions of selective IHC loss

were seen in 10 of 37 (27%) preterm ears and only 1 of 36 (3%) full-term ear (Figure 2). Eight of ten of these preterm ears showed essentially no OHC loss, while a pair showed IHC loss throughout the cochlea spiral coupled with OHC loss in the basal half of the cochlea. The IHC loss patterns tended to be symmetrical between the two ears and to be present throughout the cochlear spiral. The selective IHC loss in the one full-term case was less significant, less symmetrical between the two ears, and less extensive in its spread along the cochlear spiral.

Discussion

The most salient findings of the present study were twofold: (1) that a high percentage of ears in both preterm (41%) and full-term (28%) populations show significant hair cell loss and (2) that a remarkably high percentage of preterm ears (27%) show the relatively rare cochlear histopathology of selec-



A Normal ear;
B selective OHC loss;
C combined IHC and OHC loss;
D-F complete IHC loss with scattered or no OHC loss.

tive loss of IHCs. The high percentage of ears with hair cell loss of all types is perhaps not surprising given that sensorineural hearing loss is significantly more common in NICU survivors than in babies not requiring such intense hospital care at birth (8) and that the ears analyzed here were from the population that was so seriously ill that they did not survive the NICU stay.

Selective inner hair cell loss is a relatively rare pattern of histopathology in either human temporal bones or animal models of cochlear dysfunction (1,2,3,4). It has been reported in chinchillas treated with carboplatin (2,7), and in mice with targeted deletion of the gene for a thiamine transporter expressed only in inner hair cells (3). The present results suggest there is an elevated risk of selective inner hair cell loss in premature infants as well: 8-fold higher than in full-term ears.

A possible link between carboplatin effects and thiamine transporter effects has been suggested (3): the sulfur-containing antioxidant methionine decreases the ototoxicity of platinum compounds such as carboplatin, by the formation of sulfur-platinum adducts. Carboplatin may be ototoxic to inner hair cells because it binds to thiamine, which also contains sulfur, and leads to problems selective to IHCs in those species where the high-affinity thiamine transporter is expressed only in the IHCs, e.g., mouse and possibly chinchilla (3). If true, it is possible that this thiamine transporter is not yet fully expressed in premature IHCs, thereby leading to the selective IHC death observed here in cases of extreme systemic stress.

Selective loss of inner hair cells can result in an “auditory neuropathy” phenotype, i.e. absent auditory brainstem responses with maintenance of otoacoustic emissions, if the rest of the cochlear duct is functioning normally (6). A recent hearing screen of NICU patients (8) reports an increased incidence of “auditory neuropathy” in pre-term babies. The present study suggests that the underlying pathology may be loss of inner hair cells rather than neuronal damage.

References

1. Amatuzzi MG et al. Selective inner hair cell loss in premature infants and cochlea pathological patterns from neonatal intensive care unit autopsies. *Arch Otolaryngol Head Neck Surg* 2001; 127:629-636.

2. Liberman MC et al. Effects of selective inner hair cell loss on DPOAE and CAP in carboplatin-treated chinchillas. *Auditory Neuroscience* 1997; 3:255-268.

3. Liberman MC et al. Deletion of SLC19A2, the high affinity thiamine transporter, causes selective inner hair cell loss and an auditory neuropathy phenotype. *J Assoc Res Otolaryngol* 2006; 7:211-217.

4. Schuknecht HF. *Pathology of the Ear*, 2nd Edition. 1993; Baltimore: Lea & Febiger, 503 pp.

5. Slack RW et al. Inner hair cell loss and intracochlear clot in the preterm infant. *Clin Otolaryngol Allied Sci* 1986; 11:443-446.

6. Starr A et al. Auditory neuropathy. *Brain* 1996; 119:741-753.

7. Wake M et al. Carboplatin ototoxicity: an animal model. *J Laryngol Otol* 1993; 107:585-589.

8. Xoinis K et al. Extremely low birth weight infants are at high risk for auditory neuropathy. *J Perinatol* 2007; 27:718-723.

Acknowledgments:

Supported by grants from the National Institute on Deafness and Other Communication Disorders and the Temporal Bone Foundation. We are grateful to Prof. Jorge Pizza from the Pathology Department of the Hospital de Niños in San Jose, Costa Rica, for granting access to obtain material for this research. Figures are reproduced with permission from J Assoc Res Otolaryngology.

Correspondence to:

M. Charles Liberman, Ph.D
Massachusetts Eye & Ear Infirmary
243 Charles St.
Boston, MA 02114, USA.
Tel: 1-617-573-3745
email: charles_liberman@meei.harvard.edu

Otopathology Mini-Travel Fellowship Program

The NIDCD National Temporal Bone Registry is pleased to announce the availability of mini-travel fellowships. The fellowships provide travel funds for research technicians and young investigators to visit a temporal bone laboratory for a brief educational visit, lasting approximately one week. The emphasis is on the training of research assistants, technicians and junior faculty.

These fellowships are available to:

1. U.S. hospital departments who aspire to start a new temporal bone laboratory.
2. Inactive U.S. temporal bone laboratories that wish to reactivate their collections, or
3. Active U.S. temporal bone laboratories that wish to learn new research techniques.

Up to two fellowship awards will be made each year (\$1,000 per fellowship). The funds may be used to defray travel and lodging expenses. Applications will be decided on merit. Interested applicants should submit the following:

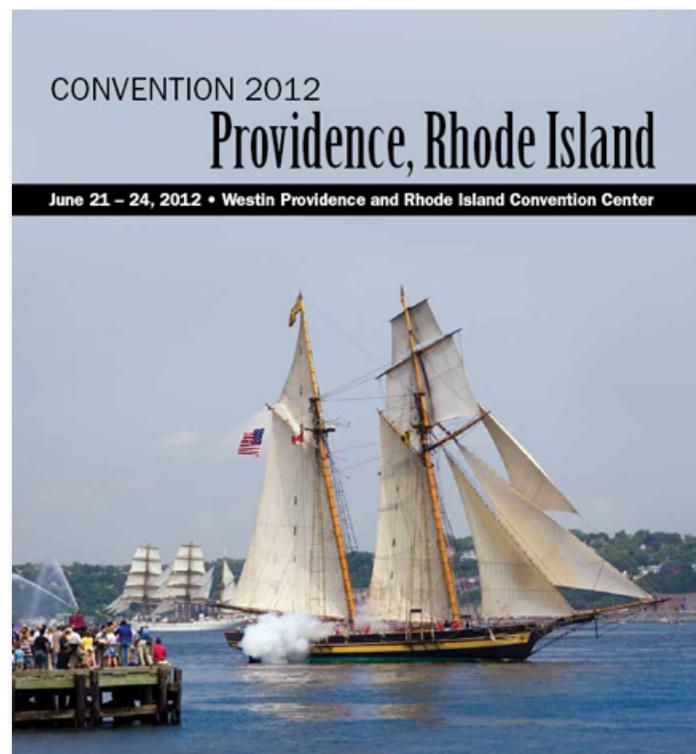
1. An outline of the educational or training aspect of the proposed fellowship (1-2 pages).
2. Applicant's curriculum vitae.
3. Letter of support from temporal bone laboratory director or department chairman.
4. Letter from the host temporal bone laboratory, indicating willingness to receive the traveling fellow.

Applications should be submitted to:

Saumil N. Merchant, M.D.
NIDCD Temporal Bone Registry
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114
saumil_merchant@meei.harvard.edu

Meetings

The Registry plans to exhibit at the 2012 Hearing Loss Association of America Convention to be held in Providence, Rhode Island.





**NIDCD National Temporal Bone, Hearing & Balance
Pathology Resource Registry**
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114-3096

NON-PROFIT ORG
U.S. POSTAGE PAID
BOSTON, MA
PERMIT NO. 53825

Address Service Requested

Free Brochures for your Office or Clinic about Temporal Bone Research and Donation

• *The Gift of Hearing and Balance: Learning about Temporal Bone Donation* is a 16-page full-color booklet which describes in more detail the benefits of temporal bone research. It also answers commonly asked questions regarding the temporal bone donation process. (Dimensions: 7"x10")

If you would like to display this brochure, please complete the form below and return it to the Registry by mail or fax. The brochures will be sent to you **free of charge**. Please circle the amount requested for each brochure or write in amount not listed.

The Gift of Hearing and Balance _____ **25 50 100**

Name: _____

Address: _____

City, State, Zip: _____

Telephone: _____

Mail or fax this form to the Registry at: **NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry
Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114
Toll-free phone: (800) 822-1327, Fax: (617) 573-3838
Email: tbregistry@meei.harvard.edu**