MENIERE’S SYNDROME: ARE SYMPTOMS CAUSED BY ENDOLYMPHATIC HYDROPS?

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INTRODUCTION

The hallmark of Meniere’s syndrome at a histopathological level is the presence of endolymphatic hydrops within the inner ear (1). In the majority cases, light microscopy of temporal bone sections has failed to demonstrate losses of sensory or neural structures within the inner ear such as hair cells, neuronal cells, stria vascularis, dark cells etc, that can be correlated with the premortem loss of auditory and vestibular function (1). Because hydrops is the only consistent pathologic abnormality observed at light microscopy, a central dogma has been articulated regarding the pathophysiology of Meniere's syndrome: although many possible etiologic factors can lead to endolymphatic hydrops, it is the hydrops that generate the symptoms of Meniere's syndrome (2) (Fig. 1). The central dogma has not been conclusively proven. If the central dogma were true, then every case of Meniere's syndrome should have endolymphatic hydrops and every case of hydrops should show the clinical symptoms, unless the chain of neural events is interrupted. A
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The NIDCD National Temporal Bone Registry will sponsor a symposium at the upcoming Association for Research in Otolaryngology (ARO) Annual MidWinter Meeting in New Orleans, LA on February 19th through 24th, 2005. Below is the list of speakers and the topics of their presentations. For more information about the symposium please visit the ARO website at www.aro.org.

Moderator: Elizabeth Keithley, Ph.D.
University of California, San Diego

Richard J. Smith, M.D.
University of Iowa Hospital & Clinics
Hereditary Hearing Loss in the Human - Where are we in 2005?

Saumil N. Merchant, M.D.
Massachusetts Eye and Ear Infirmary-Harvard Medical School
Histopathologic Phenotypes of Genetic Deafness in Humans

Jian Zuo, Ph.D.
St. Jude Children’s Research Hospital
A Molecular Geneticist’s View of Mouse Models for Genetic Deafness

M. Charles Liberman, Ph.D.
Massachusetts Eye and Ear Infirmary-Harvard Medical School
Structure-Function Correlations in Mouse Models of Genetic Deafness

Karen P. Steel, Ph.D.
Wellcome Trust Sanger Institute
Mouse Models of Usher Syndrome

Rick A. Friedman, M.D., Ph.D.
House Ear Institute
Mouse Models of Brancio-oto-renal (BOR) syndrome

Thank you

Thank you to all the participants of the meeting of the Association of Late-Deafened Adults (ALDA) who visited the Registry’s booth at the 2004 ALDA Convention in Burlington, Vermont in September. Many registered donors as well as new potential donors stopped by our exhibit. Thank you all for your hospitality.

Deafness Research Foundation Announces Changes

The DRF has announced a change of their contact information. Their new information is listed below. Please visit their website for further details.

New contact information:
8201 Greensboro Dr, Ste 300, McLean, VA 22102
Phone 703-610-9025 Fax 703-610-9005 or
e-mail: info@drf.org and website: www.drf.org
Brochures about Temporal Bone Research and Donation Order Free-of-Charge for Your Office, Clinic or Organization

The NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry, which is dedicated to promoting research on hearing and balance disorders through the study of temporal bones, has published two informational brochures, which you may request for display in your office and/or waiting rooms. Both brochures encourage individuals with hearing or balance disorders to bequeath their temporal bones to scientific research.

That Others May Hear is a short form brochure which describes briefly the functions of the Registry, and answers commonly asked questions regarding the temporal bone donation process. (Dimensions: 9” x 4”)

The Gift of Hearing and Balance: Learning about Temporal Bone Donation is a 16-page, full-color booklet which describes in more detail and with diagrams, the structure of the ear, types of auditory disorders, the microscopic study of the temporal bone, and the benefits of temporal bone research. It also answers commonly asked questions regarding the temporal bone donation process. (Dimensions: 7” x 10”)

If you are willing to display either or both of these brochures, 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.

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Mail or fax this form to the Registry at:
NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry
Massachusetts Eye and Ear Infirmary
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Or submit your request using email: tbregistry@meei.harvard.edu
temporal bone study from our laboratory in 1989 to assess the correlation between case histories and post-mortem histopathology in Meniere’s syndrome raised questions about the validity of this central dogma (3). Since this 1989 study, we have added over 250 new temporal bone specimens to our collection. The goal of this study was to re-examine the relationship between hydrops and symptoms of Meniere’s syndrome by including the new specimens.

METHODS

The human temporal bone collection at the Massachusetts Eye and Ear Infirmary currently contains 1,750 specimens from 963 individuals. A search of the database containing the records of our temporal bones was conducted in two ways: a) Searching for cases with a clinical diagnosis of Meniere’s syndrome. A clinical diagnosis of Meniere’s syndrome was made when the case history included both episodic vertigo and sensorineural hearing loss. b) Searching for cases with a histopathological description of endolymphatic hydrops in at least one ear. Endolymphatic hydrops was defined for the purpose of this study as hydrops present in any part of the membranous labyrinth with the exception of apical cochlear hydrops (1). The hydrops was characterized as “idiopathic” when there was no obvious pathology in the temporal bone that could be considered causal, or as “secondary”, based on the co-existence of other pathologic changes in the inner ear such as surgical trauma, temporal bone fracture, labyrinthitis, syphilis, Cogan’s syndrome and a variety of neoplasms affecting the labyrinth (1). The case histories and histologic slides of specimens that met the above criteria were reviewed to examine the relationship between hydrops and symptoms.

RESULTS

1. Searching for a clinical diagnosis of Meniere’s syndrome

Twenty eight cases had a clinical diagnosis of Meniere’s syndrome. Every patient with this diagnosis had endolymphatic hydrops on histopathologic examination in the affected ear. The hydrops was idiopathic in 26 cases, and considered secondary in 2 cases. All 26 cases with idiopathic hydrops showed dilatation of the cochlear duct and the saccule, and the majority (17 cases, 65%) also had hydrops involving the utricle and/or the ampullae.

2. Searching for a histopathological description of endolymphatic hydrops

Seventy nine cases were identified as having endolymphatic hydrops in at least one ear, of which 35 cases were idiopathic and 44 were secondary. Of the 35 cases with idiopathic hydrops, 26 cases had a clinical history of Meniere’s syndrome, while 9 cases did not. None of the 9 individuals had a history of episodic vertigo, despite hydrops of the cochlea and/or the vestibular apparatus. One case had normal hearing and the temporal bones showed saccular hydrops on both sides. The remaining 8 cases had varying degrees of sensorineural hearing loss, which was fluctuating, sudden or progressive in nature. The audiometric pattern of the loss was variable, and included low tone, flat and downsloping patterns. The hydrops was limited to the cochlea in 1 case, while the other 7 cases had hydrops affecting the cochlea, saccule and utricle (± ampullae). The severity and extent of hydrops in these 7 cases was similar to that observed in the 26 cases with Meniere’s syndrome. Many specimens with idiopathic hydrops also demonstrated pre-mortem ruptures of the membranous labyrinth. Some of the 9 cases with idiopathic hydrops showed partial losses of hair cells and/or afferent neurons within the cochlear and vestibular end organs. However, none of the ears showed severe or total degeneration of the end organs (such degeneration would confound the interpretation of the role of hydrops in causing symptoms).

An analysis of the 44 cases with secondary hydrops revealed: (a) Only 2 individuals had the Meniere symptom complex during life. (b) There were 10 cases without a history of episodic vertigo. The hydrops involved only the cochlea in 2 cases, while the remaining 8 had cochleosaccular hydrops (± hydrops affecting the utricle and ampullae). The extent and severity of hydrops in these 8 cases was similar to that observed in bones from individuals with Meniere’s syndrome, including the presence of ruptures affecting the membranous labyrinth in several bones. All 10 cases exhibited varying degrees of sensorineural hearing loss in the hydropic ear. However, none of the 10 cases had severe or complete atrophy of the auditory or vestibular end organs. (c) There were an additional 32 cases without an accompanying history of symptoms
of Meniere’s syndrome, but no firm conclusions could be drawn about the relationship between hydrops and the absence of symptoms in these cases, because of confounding factors such as degeneration of the end organs, inadequate medical records or young age of the subject (which might preclude reporting of vertigo or hearing loss).

DISCUSSION

Our results indicate that (a) endolymphatic hydrops of the cochlea is invariably associated with a sensorineural hearing loss, but not necessarily a fluctuating type or a low-tone pattern, and (b) hydrops of the cochlea and/or vestibular system is not necessarily associated with a history of episodic vertigo. Therefore, these results are not consistent with the central dogma of hydrops as the final common pathway for production of symptoms in Meniere's syndrome. The results are more consistent with hydrops being a marker for disordered homeostasis of the labyrinth, wherein some factor (as yet unknown) produces both the clinical symptoms of Meniere's syndrome and endolymphatic hydrops. The results of the present study are similar to that of the previous temporal bone study from our laboratory in 1989 regarding the relationship between hydrops and symptoms (3). The present study included the additional temporal bone cases accrued over the last 15 years, as well as cases with secondary hydrops. A review of the literature reveals reports of cases with asymptomatic hydrops (4-7), as well as cases of Meniere's syndrome diagnosed during life without demonstrable hydrops at histology (6,8-12). The central role of hydrops in mediating the pathophysiology of the Meniere symptom complex has also been questioned by other authors (13,14).

Much research has focused on the pathology and pathophysiology of hydrops in the guinea pig model, in an attempt to better understand Meniere’s syndrome. Although it had been traditionally assumed that the hydrops was the result of blockage of longitudinal flow of endolymph from the cochlea to the endolymphatic sac (1,15), measurements of the rate of endolymph flow in the guinea pig showed the rate of longitudinal flow to be exceedingly small and inadequate to account for the development of hydrops (16). Thus, the mechanism of how hydrops occurred after blockage of the endolymphatic duct remained unknown. The cause of auditory threshold shifts in hydropic animals also remained obscure and was attributed as being the result of the hydrops (1,17).

New light was shed upon the histopathology of hydrops in the guinea pig by the findings of Ichimiya et al (18) and Nadol et al (19), who demonstrated cytochemical and ultrastructural lesions at the level of hair cells, cochlear neurons and the spiral ligament. The essence of their investigations was that the type I fibrocytes of the spiral ligament were the most severely affected cochlear cells, although type II fibrocytes were also clearly affected in animals with long term survivals. However, it was not known which came first -- the hydrops or the cytopathological changes, raising the question as to whether hydrops had induced the observed abnormalities or vice versa. More recently, Shinomori et al extended these findings to show that the cytochemistry of fibrocytes and other non-sensory cells changed before the induction of hydrops (20). Shinomori et al blocked the endolymphatic duct to induce hydrops in 22 guinea pigs and studied the cytochemistry of the inner ear at various post-operative survival times ranging from 1 day to 3 months. A striking finding was that there were changes in the cytochemistry of type I and type II fibrocytes, and of non-sensory epithelial cells one day after surgery, before the development of hydrops. The type I fibrocytes showed increased immunostaining for the NaK2Cl co-transporter (NKCC1), along with decreased immunostaining for taurine and C-Jun-N-terminal kinase (JNK).

These results are interesting because the fibrocytes of the spiral ligament, which contain a variety of gap junctions, enzymes and proteins, are known to play crucial roles in maintaining fluid homeostasis within the cochlea (21-24). For example, the type I and type II fibrocytes are involved in the transport of K+ ions from the root cells to the stria vascularis, thus enabling the recycling of K+ ions within the scala media (21,23). NKCC1 is involved in regulation of cellular volume in response to osmotic stresses (25). Taurine is an amino acid that widely serves as an osmolyte (26). JNK is known to be a critical player in many forms of cellular stress responses (27). The increased immunostaining for NKCC1 and decreased staining...
for taurine in the Shinomori et al study suggest that the type I fibrocytes were osmotically stressed and that the cytochemical changes reflected compensatory mechanisms for regulation of cell volume. The decrease in staining for JNK indicates that the fibrocytes were under stress probably due to a change in perilymphatic conditions induced by the surgical procedure. The connective tissue surrounding the endolymphatic duct is in communication with the perilymphatic fluid spaces of the vestibular and cochlear end organs (28). We hypothesize that surgical obstruction of the endolymphatic duct altered the cytochemistry of the perilymph (in some unknown manner), resulting in cellular stress and dysfunction of fibrocytes of the spiral ligament. In turn, this may have interfered with the recycling of K+ ions, resulting in an osmotic imbalance and expansion of the endolymphatic compartment, i.e., endolymphatic hydrops. In other words, the findings suggest that hydrops is the result (rather than the cause) of disordered cochlear homeostasis. There is another line of evidence to support the hypothesis that dysfunction of the spiral ligament results in endolymphatic hydrops. Transgenic mice with deletion of the Brn-4 transcription factor which is expressed in fibrocytes of the spiral ligament develop endolymphatic hydrops (29,30). These animals also suffer from a hearing loss and show decreased immunoreactivity for NaK-ATPase, NKCC1 and connexin-31 within the type II fibrocytes of the ligament (30).

Much remains to be clarified regarding the underlying cytological changes that lead to the induction of hydrops. The key point of the discussion is that there is a pressing need for a search for the cellular and molecular bases of the various symptoms of Ménière’s patients because the evidence indicates that hydrops per se is not the cause. Therefore, therapeutic strategies whose main goal is the reduction of hydrops (such as endolymphatic sac shunting, sacculotomy, etc.) are unlikely to control the disorder. A better understanding of the syndrome at a cellular level may uncover targets for novel therapeutic interventions.

CONCLUSION

Endolymphatic hydrops should be considered as a histologic marker for Ménière's syndrome rather than being directly responsible for its symptoms.

REFERENCES

22. Spicer SS, Schulte BA. The fine structure of spiral limaent cells relates to ion return to the stria and varies with place-frequency. Hear Res 1996;100:80-100.

A part of this study was presented at the Scientific Meeting of the American Otological Society in May 2004, and is in press in Otology and Neurotology. Reproduced with permission.

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New Book Available

“I’ve Lost My What???: A Practical Guide to Life After Deafness”

By: Shawn Lovely

“I’ve Lost My What???” is a new book written by Shawn Lovely, former secretary of the Association of Late-Deafened Adults (ALDA). The book deals with the challenges faced by an individual in all aspects of life including relationships with family and friends, as well new methods of communication such as cochlear implants and hearing aids.

The reader will get a feel for the daily obstacles faced by many late-deafened individuals. Communication options such as assistive listening devices, hearing aids and cochlear implants are discussed. Contact information is provided about organizations and agencies that may be of interest to individuals with hearing impairment.

The book is well suited for people who have lost their hearing as well as family, friends or co-workers of late-deafened adults. All royalties from the sale of the book are donated to the ALDA organization.

The book can be purchased online through the publisher at www.iUniverse.com or by calling 1-877-288-4737 (toll-free, voice). The book is also available online at Amazon or Barnes and Noble websites.