International Tinnitus Journal, Vol. 12, No. 1, 75–81 (2006)

Brain and Inner-Ear Fluid Homeostasis, Cochleovestibular-Type Tinnitus, and Secondary Endolymphatic Hydrops

Abraham Shulman[1] and Barbara Goldstein[2]

[1]*Health Science Center at Brooklyn and* [2]*Department of Otolaryngology, State University of New York, Downstate Medical Center, Brooklyn, and Martha Entenmann Tinnitus Research Center, Forest Hills, New York*

Abstract: Secondary endolymphatic hydrops (SEH) has clinically been found to have a significant incidence of occurrence in patients with subjective idiopathic tinnitus (SIT) of a severe disabling type. The diagnosis is made clinically and has been established by integration in a medical audiological tinnitus patient protocol of the clinical history with results of electrodiagnostic cochleovestibular testing that fulfill the diagnostic criteria of inner-ear disease consistent with Ménière's disease. SEH is hypothesized to be a factor, not an etiology, influencing the clinical course of SIT. Alterations over time (i.e., delay in the homeostatic mechanisms in normal function of the fluid compartments of the inner-ear perilymph, endolymph, or brain cerebrospinal fluid) result in endolymphatic hydrops and interference in normal function of the inner ear, with resultant inner-ear complaints that can be highlighted by tinnitus rather than by vertigo. The endolymphatic hydrops may be either localized or diffuse within the cochlear or vestibular labyrinth. The etiologies and mechanisms of cochleovestibular-type tinnitus are multiple and are influenced by the SEH. Classically, the tetrad of symptoms—episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and ear blockage—associated with the histopathological correlate endolymphatic hydrops has been diagnosed as Ménière's disease. Specifically, key etiological agents that have been identified as playing a role in the clinical course of tinnitus (e.g., noise exposure, stress) may serve as "triggers" or stressors (or both), resulting in interference in normal biochemical and physiological function of sensorineural structures in the inner ear or in neural structures in the brain. In both conditions, the alterations over time (i.e., delay) in the clinical manifestation of the tetrad of symptoms of inner-ear dysfunction, when highlighted by SIT rather than vertigo, otherwise fulfill the criteria for diagnosing SEH. The chief complaint of SIT, when presenting as one of the tetrad of inner-ear symptoms and otherwise diagnosed as Ménière's disease, has also been associated clinically with perfusion asymmetries in brain, identified by nuclear medicine brain imaging (single-photon emission computed tomography [SPECT] of brain), and reflects an interference in homeostasis in the blood-brain labyrinth or blood-brain barriers, with a resulting SEH. The medical significance of the SIT in some patients may be a gradual, progressive sensorineural hearing loss. The inclusion of SPECT of brain in SIT patients demonstrates a global approach for improving the accuracy of diagnosing the SIT symptom, for focusing on the contribution of central nervous system dysfunction to the development of SEH, and for understanding and influencing the clinical course of SIT.

Key Words: blood-labyrinth; brain-labyrinth; homeostasis; medical audiological tinnitus patient protocol; medical significance; secondary endolymphatic hydrops

Reprint requests: Dr. Abraham Shulman, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Box 1239, Brooklyn, NY 11203. Phone: 718-773-8888; Fax: 718-465-3669; E-mail: metrc@inch.co

This study updates our understanding of secondary endolymphatic hydrops (SEH) on the basis of our clinical experiences with the symptom of subjective idiopathic tinnitus (SIT), particularly of a severe disabling type. In more than 8,500 patients seen in the years 1979–2005, we clinically identified SEH as having a significant incidence of occurrence and serving as a factor influencing the clinical course of SIT [1].

The identification of SEH and its significance for tinnitus treatment and control was reported originally in a SIT study that was performed in 1979 as an attempt to establish the incidence of occurrence of a vestibular abnormality in SIT patients [2]. SIT patients were differentiated by their clinical histories as to whether they were symptomatic or nonsymptomatic for an accompanying symptom of vertigo. A significantly increased incidence of positive vestibular dysfunction of the peripheral vestibular labyrinth consistent with the involved side of the SIT was found in both groups on the basis of testing using a vestibular test battery and electronystagmography [3,4]. An additional study using a computerized rotary chair and pursuit tracking system confirmed this observation [5].

The nuclear medicine brain-imaging technique—single-photon emission computed tomography (SPECT)—of brain in SIT patients has improved the accuracy of the SIT diagnosis and attempts for tinnitus relief. Since our original presentation and publication of this clinical experience [1–5], the clinical translation of advances in understanding inner-ear physiology and biochemistry and identification by SPECT of brain of perfusion asymmetries in multiple regions of interest in brain (reflecting underlying neurochemistry of brain function and dysfunction) are considered to support a central nervous system (CNS) contribution to the development of SEH in some SIT patients.

This study reviews the history of delayed SEH, examines its role in the clinical course of tinnitus, discusses a hypothesis of its development, and tracks its relationship to the tetrad of inner-ear symptoms that, when they occur with episodic vertigo as the chief complaint, are frequently diagnosed as Ménière's disease (MD). A case report will demonstrate clinical support for the hypothesis regarding its development.

HISTORY OF (DELAYED) SEH

Guild [6] suggested in 1927 that the endolymphatic sac (ES) may be involved with dysfunction or dysregulation of the inner ear and that the ES may play an important role in normal metabolic activity of the inner ear. In 1938, Hallpike and Cairns [7] identified endolymphatic hydrops (EH) in the temporal bone, and EH has subsequently been accepted as a histopathological correlate of MD, a clinical syndrome manifested as a tetrad of inner-ear complaints: episodic vertigo, gradual, progressive sensorineural hearing loss, tinnitus, and ear blockage. Unfortunately, the diagnoses of MD and EH have been used interchangeably by many.

In 1861, Ménière described a symptom complex that he considered to be a reflection of an "apoplexy" [8]. Originally, this symptom complex described by Ménière was characterized by tinnitus, hearing loss, and episodic vertigo. Delayed SEH was described by Nadol et al. [9] and by Wolfson and Lieberman [10]. Schuknecht [11,12] established a hypothesis regarding the pathogenesis of delayed episodic vertigo. He considered that vertigo can occur after an insult to the labyrinth, resulting in total deafness but preserving vestibular function or as a delayed atrophy or fibrous obliteration of the endolymphatic resorptive system, specifically the ES and the vestibular aqueduct. The contralateral ear may be also affected—that is, when one ear becomes deaf due to viral infection in early childhood, it may reflect a subclinical viral infection that eventually causes an ear with normal hearing to develop over a long period the EH that is similar to that of MD.

Kamei et al. [13] reported the first clinical cases that became a basis for establishing delayed EH as a concept and, in 2004, Kamei reviewed his clinical experience of delayed or SEH as a clinical entity [14]. The views of Schuknecht [11,12] regarding MD and EH and SEH have been widely supported up to and including the present. However, a lack of reporting examination of temporal bone histopathology raises difficulty for diagnosis in explaining ipsilateral SEH today. Merchant [15] has reviewed inconsistencies between the clinical diagnosis of MD and temporal bone studies of patients with diagnosed MD.

Since 1979, Shulman [1] has reported SEH to have a significant incidence of occurrence in patients with a chief complaint not of vertigo but of SIT of a severe disabling type. The clinical translation of the concept of SEH for SIT has resulted in significantly increased accuracy for the SIT diagnosis and efficacy of modalities of treatment attempting tinnitus relief.

HYPOTHESIS

SEH is hypothesized to be a factor—not an etiology—influencing the clinical course of SIT. Alterations over time (i.e., delay) in the homeostatic mechanisms in normal function of the fluid compartments of the inner-ear perilymph or endolymph or in brain cerebrospinal fluid (CSF) result in EH and interference in the normal function of the inner ear, with resultant inner-ear complaints that can be highlighted by tinnitus rather than by ver-

tigo. The EH may be either localized or diffuse within the cochlear or the vestibular labyrinth (or both). The etiologies and mechanisms of cochleovestibular-type tinnitus are multiple and are influenced by the SEH.

Classically, the tetrad of symptoms—episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and ear blockage—associated with the histopathological correlate EH has been diagnosed as MD. Specifically, key etiological agents that have been identified as playing a role in the clinical course of tinnitus (e.g., noise exposure, stress) may serve as a "trigger" or stressors, resulting in interference in normal biochemical and physiological function of sensorineural structures in the inner ear or in neural structures in the brain. In both conditions, the alterations over time (i.e., delay) in the clinical manifestation of the tetrad of symptoms of inner-ear dysfunction (when highlighted by SIT rather than vertigo) otherwise fulfill the criteria for diagnosis of SEH.

The medical significance of the SIT in some patients may be a gradual, progressive sensorineural hearing loss. The inclusion of SPECT of brain in SIT patients demonstrates a global approach for improving accuracy in diagnosing the SIT symptom, focusing on the contribution of CNS dysfunction to the development of SEH, and for understanding and influencing the clinical course of SIT. The classical concept of MD was that dysfunction of the ES is followed by obstruction of the longitudinal flow of endolymph, resulting in EH and the tetrad of MD symptoms.

Attempts to identify histopathological correlates of SEH have failed to demonstrate consistent findings of EH in temporal bones of affected patients. Inconsistencies have been identified among the tetrad of complaints associated with the diagnosis of MD, the findings of presence or absence of EH, and the lack of consistency of findings of EH in temporal bone studies of patients with previously diagnosed MD. This has led to attempts to translate recent advances in sensorineural cochlear physiology for the understanding of EH production, focusing on the role of the ES and fluid compartments of the inner ear, to explain the clinical course of the tetrad of complaints identified with the diagnosis of MD. The classical hypotheses proposed for EH and SEH is considered to be limited by what is and is not known of perilymph and endolymph production. The site of production of perilymph and endolymph is still in question.

Schuknecht [12] reported a direct fluid pathway for perilymph from the scala tympani to the organ of Corti via the canaliculi perforantes, small openings in the osseous spiral lamina, and patency of the cochlear aqueduct. Classically, the manner of perilymph production has remained elusive. Theories of perilymph production have been related to CSF production. Perilymph, like other extracellular fluids, is produced as a blood ultrafiltrate [16]. The high $Na+$ and low $K+$ content of the perilymph is controlled by local homeostatic mechanisms and by radial flow through the cochlea [17].

In reporting on the blood-labyrinth barrier (BLB) and fluid dynamics of the inner ear, Juhn et al. [16] reported that under normal conditions, the inner ear possesses stable homeostatic mechanisms for maintaining functional integrity of the inner-ear fluids. The inner-ear fluid homeostasis is maintained by a variety of regulatory mechanisms, including an ion transport system controlled by the stria vascularis and spiral ligament, a BLB, and a constant blood supply. Disturbance in any one of the mechanisms induces the disruption of homeostasis as expressed by ionic, osmotic, or metabolic imbalance between the compartments. Such membrane displacement or functional disturbances in the inner ear can serve as a triggering mechanism for abrupt function disturbances seen in such diseases as MD, sensorineural hearing loss, tinnitus, and presbycusis [16].

Animal experiments indicate that the ES is a metabolically active filter for the endolymphatic system. Initial damage results in hydrops, followed by more diffuse distortion of the membranous labyrinth involving degeneration in structures of the organ of Corti, stria vascularis, and cochlear neurons and lesser degenerative changes in the vestibular sensor organs.

Endolymph, like perilymph, was once reported to be an ultrafiltrate of blood. Now it is known to be derived from transcellular diffusion of perilymph and maintained by metabolic processes. Also, it may be secreted and absorbed by the various inner-ear structures (i.e., stria vascularis, planum semilunatum, spiral prominence, and ES) [18].

Recent reports of the function of the spiral ligament in response to stress have been published [19–21]. The BLB consists of tight junctions within capillaries of the spiral ligament. The tight junctions form the morphological site of the BLB and prevent passage of substances from blood into the fluid of the inner ear. It is less permeable to several ions and differentially modulates the passage of larger substances in proportion to molecular weight [22]. The existence of a tight BLB, equivalent to the blood-brain or blood-CSF barriers, has been confirmed [23].

Endolymph production has been theoretically considered to be related to the function of the stria vascularis. Experimental obstruction of the endolymphatic duct in the guinea pig results in functional changes in the spiral ligament. The spiral ligament responds to stress within the cochlea. Dysfunction of the spiral ligament results in biochemical and metabolic abnormalities of inner-ear fluids, with secondary dysfunction of hair cells and neurons. EH is a byproduct of this process [15]. In general, the blood-brain barrier is a series

of interfaces between arterial blood, CSF, and neural tissue that regulates the transport of chemical substances. It controls cerebral homeostasis.

The issue of alteration in homeostasis within the fluid compartments of the inner ear or CSF of brain has raised the question as to whether some cases presenting with the predominant symptom of tinnitus may be a result of alteration in the fluid volume of the membranous compartments of the inner ear (i.e., EH, local or diffuse) secondary to the effects of CSF on the perilymph compartment of the inner ear [1].

Stress-related hormones have an effect on inner-ear fluid homeostasis and function [24]. Some have suggested that a stress reaction in the area of the spiral ligament may be related to alteration or fluctuation in intracerebral CSF pressures, frequent in patients with fluctuating hypertension. Emotional stress or severe anxiety is known to precipitate symptoms of MD. The effect of epinephrine and steroid hormones can lead to increased intracellular calcium. Epinephrine infusion results in adrenergic receptor stimulation at the cell membrane of epithelial cells in the lateral wall of the cochlea. Gene defects are seen in neurological diseases as episodic ataxia. They may occur in patients with inner-ear disease, such as MD, which may explain the increased susceptibility of patients with MD, owing to the effects of stress, as compared to those without a disease [25].

Support for the concept and hypothesis that alterations between CSF and the labyrinth may be related to EH have until now focused on the BLB. Disturbances to the BLB in the form of hormonal modulation by alteration of membrane permeability of ions and water have been reported [26]. Similar ionic equilibrium changes in perilymph and endolymph are induced by ototoxic drugs, systemic injection of urea, or glycerol. A shift in water out of the endolymphatic space into blood results in an increase in endolymph osmolality, disrupting the local ionic homeostasis. Systemic administration of steroid—epinephrine—has demonstrated an increase in perilymph osmolality and altered cochlear physiology [27,28].

In summary, an intimate relationship has been shown to exist between perilymph and endolymph and perilymphatic tissue and CSF, all having an effect on the perilymph and endolymph.

We consider that although no single theory that has been posited adequately defines the role of the BLB or blood-brain barrier in the development of inner-ear pathological processes, the basic science experiments that have been identified with the electron microscope, the reported morphological changes in inner-ear structures, and our clinical experience with SIT support this association.

CASE REPORT

Since 1989, nuclear medicine imaging of brain with SPECT has been introduced to improve the accuracy of tinnitus diagnosis and to monitor the efficacy for modalities of therapy attempting tinnitus relief. In a patient classically fulfilling the criteria for MD but resistant to treatment for vertigo, we identified significant alterations in brain perfusion. The patient was a 48-year-old man who presented with the chief complaints of constant ear blockage of fluctuating intensity in the right ear, citing 3 weeks' duration, and occasional unsteadiness. Neurootological evaluation, including cochleovestibular testing, was the basis for a diagnosis of MD. Treatment included diuretic, antihistamine, and antihypertensive medication. Persistence of the complaints, highlighted by imbalance, was the basis for neurological consultations and magnetic resonance imaging of the brain and internal auditory canals with gadolinium, results of which were reported as negative, with the exception of mild cortical atrophy, and followed by SPECT of brain and baseline and Diamox stress tests [29].

Baseline results of SPECT of brain showed significant perfusion asymmetries, particularly on the right globally, suggesting findings compatible with cerebrovascular small-vessel disease. Resultant Diamox findings were compatible with multifocal cerebral diaschisis or neuronal loss, predominantly in the right hemisphere.

A "watershed effect" was demonstrated in this patient by a linear-appearing defect in the frontal lobe, greater on the right than on the left. The vascular supply to the frontal lobe areas proceeds from the frontal branches of the middle cerebral artery and the anterior cerebral artery. Such a defect reflects the most distal part of circulation in major arteries, the arteriolar capillary junction. Such an area is known as the *watershed.* It is an effect demonstrated by SPECT for areas of hypoperfusion in brain, which reflects the arteriolar capillary junction of two or more patent arteries in a particular region of interest in the brain. It is a characteristic distribution of ischemia.

We considered this case report to support the hypothesis that an alteration in homeostasis in the fluid compartments between brain and inner ear can result in a change of the osmolality of the endolymphatic duct by conditions in the perilymph. When coupled with a stress reaction in the area of the spiral ligament, the overall effect is an increase in endolymph (i.e., EH). In patients presenting with the inner-ear symptoms highlighted by tinnitus, the SIT and the EH may very well be the "softest" of signs of inner-ear dysfunction, reflecting alterations of homeostasis both within the inner ear and between brain and ear.

In summary, alterations in the homeostatic mechanisms within the blood-brain barrier and BLB may by various mechanisms result over time in EH. Clinically, inner-ear complaints can be highlighted by a cochlear-type tinnitus. Cochleovestibular testing to its limits, when correlated

with the clinical history, has been found to fulfill the classical diagnostic criteria of SEH.

DISCUSSION

Some SIT patients who clinically present with a tetrad of inner-ear complaints may be reflective of interference in the homeostatic mechanisms of the blood-brain barrier and BLB involved in normal function of the ear and brain.

Certain factors should be considered, the first of which are MD, EH, SEH, and blood-labyrinth-brain barriers. The present conceptualization and clinical understanding of the complaints of hearing loss, tinnitus, vertigo, and ear blockage alone or in combination and identified with EH may not always be limited to peripheral vestibular dysfunction. EH in some patients may reflect the peripheral extension of alterations in the hemodynamics within the CNS. A valid question is: How many patients with diagnosed classical MD are a reflection of primary CNS disease?

As regards tinnitus, the symptom of SIT may in some patients be a "soft" sign of gradual, progressive cerebrovascular disease and early neuronal loss, with involvement of both the peripheral and central cochleovestibular systems [29,30]. Clinical types of tinnitus have been identified. Vestibular tinnitus was described in 1991 as a clinical type of tinnitus reflecting dysfunction of the vestibular labyrinth [31]. Tinnitus patients may be symptomatic or nonsymptomatic for the symptom of vertigo or other types of balance disorders. SEH has been reported, in our experience, to have an incidence of occurrence of ±25–35% [2].

Some have speculated that the clinical entity of SEH identified in tinnitus patients with vestibular tinnitus has a medical significance for both treatment and hearing conservation. The clinical contention is that subgroups of vestibular tinnitus, peripheral or central in location, potentially exist [32].

In the SPECT of brain case report, SPECT of brain demonstrated significant CNS perfusion asymmetries associated with cerebrovascular disease in a tinnitus patient with vertigo. Before SPECT of brain examination, the patient fulfilled the classical diagnostic categories of MD. The diagnosis of EH in relation to the clinical history of fluctuating hypertension introduces the clinical consideration that in this patient, the EH is delayed or secondary and that the tinnitus complaint and resistance to medical treatment for the vertigo had, for the patient, a medical significance that transcended that of only an inner-ear complaint reflective of alteration in the homeostatic mechanisms involved in the fluid compartments of both ear and brain (i.e., blood-labyrinth-brain barriers). The medical significance of the tinnitus in the right ear and the balance complaint in this patient is suggested to be one of cerebrovascular disease that is more pronounced on the right than on the left, with involvement of the right inner ear [29].

The SPECT findings suggest the existence in tinnitus patients of a state of central disinhibition over broad cortical levels [30–32]. The findings further support the original speculation that in some patients, tinnitus can originate at the site of a vestibular dysfunction, peripheral or central, and reflect the presence of subtypes of vestibular tinnitus [29,32].

In the clinical evaluation of brain perfusion asymmetry with SPECT of brain, one must differentiate between perfusion asymmetries compatible with lack of vascular reserve and neuronal loss [33]. Diaschisis is a neuronal disconnect effect, not a vascular effect. Longstanding vascular effects may result in neuronal loss. Diamox, a diuretic, is also a vasodilator that provides a test for cerebrovascular reserve.

The relationship between the fluid compartments of the inner ear, perilymph and endolymph, and the CSF of the brain has long been speculated. Support for the association of ear complaints with alterations in CSF homeostasis has been reported on the basis of clinical experience with patients presenting with the diagnoses of MD and perilymphatic fistula [34]. The two conditions can resemble each other and at times are indistinguishable one from the other. In both, the tetrad of complaints associated with MD is present. A patent cochlear aqueduct has been suspected to be present with a perilymphatic fistula in the round window or oval window or both. Cochlear aqueduct patency is most likely related to the inner-ear symptoms of hearing loss, balance problems, tinnitus, and ear fullness.

Patency of the cochlear aqueduct in all decades of life has been reported [35]. Although the patency of the cochlear aqueduct tends to decline in each decade of life, more than 20% of patients were found to have a patent aqueduct in the sixth decade. The cochlear aqueduct patency has been identified and confirmed in all age groups as declining by decades [36].

In cases wherein perilymphatic fistulas have been recurrent, lumbar puncture has revealed pseudotumor cerebri or benign intracranial hypertension [37]. Significant tinnitus relief has been accompanied by local closure of perilymphatic fistula plus lumbar puncture or lumbar peritoneal shunt of CSF. The treatment of lumbar puncture with or without lumbar peritoneal shunt tends to lower CSF pressure. This was found also to improve the success rate for repair of the perilymphatic fistula. We have considered that further improvement can be achieved by cochlear aqueduct blockage or a ventricular peritoneal shunt.

Alteration of CSF pressure by the administration of Lasix or an osmotic diuretic of some other kind and by

performing lumbar puncture with or without a ventricular peritoneal shunt has been reported to result in improvement of both tinnitus relief and other symptoms of hearing loss and vertigo and to increase efficacy for local repair techniques for perilymphatic fistula. Occasionally, performance of a lumbar puncture has revealed a diagnosis of benign intracranial hypertension or pseudotumor cerebri.

In summary, the CSF is hypothesized possibly to influence the perilymphatic space and perilymph production either by direct communication via the cochlear aqueduct, the canaliculi perforantes of the spiral osseous ligament, or by alterations in homeostatic mechanisms influencing the permeability of the blood-brain barrier and BLB. This is to be considered when discussing perilymph formation as an ultrafiltrate of blood. The clinical observations and response to treatment for complaints of hearing loss, vertigo, tinnitus, and ear blockage reported by control of perilymphatic fistula with and without lumbar puncture and by alteration of CSF pressure supports consideration of this hypothesis.

CONCLUSION

SEH has been found to have a significant incidence of occurrence in patients with tinnitus of the severe disabling type. The medical significance of SEH and the symptom of tinnitus may in some patients be a gradual, progressive sensorineural hearing loss. Disturbances in homeostatic mechanisms over time (i.e., delayed) involving the fluid compartments of the inner ear and brain may result in alterations in perilymph and endolymph, with resultant delayed EH and inner-ear complaints of hearing loss, tinnitus, vertigo, and ear blockage.

Classical diagnostic criteria of MD and SEH are clinical diagnoses established and supported by electrophysiological correlates of cochleovestibular function. Nuclear medicine imaging provides a basis for improvement in the accuracy of the tinnitus diagnosis, for its medical significance, and for a method to monitor the efficacy of modalities of therapy attempting tinnitus relief.

ACKNOWLEDGEMENTS

The authors gratefully express their appreciation to the Martha Entenmann Tinnitus Research Center, Inc., for support of this educational and research effort.

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