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Fluid Dynamics Vascular Theory of Brain and Inner-ear Function in Traumatic Brain Injury: A Translational Hypothesis for Diagnosis and Treatment

Abraham Shulman[1,3] and Arnold M. Strashun[2]

Departments of [1] Otolaryngology and [2] Radiology and Nuclear Medicine, Health Science Center at Brooklyn, State University of New York, Downstate Medical Center, Brooklyn, and [3] Martha Entenmann Tinnitus Research Center, Forest Hills, New York, USA

Abstract: It is hypothesized that in all traumatic brain injury (TBI) patients with a clinical history of closed or penetrating head injury, the initial head trauma is associated with a vibratory sensation and noise exposure, with resultant alteration in vascular supply to the structures and contents of the fluid compartments of brain and ear (i.e., the fluid dynamics vascular theory of brain–inner-ear function [FDVTBE]). The primary etiology—head trauma—results in an initial fluctuation, interference, or interaction in the normal fluid dynamics between brain and labyrinth of the inner ear, with a resultant clinical diversity of complaints varying in time of onset and severity. Normal function of the brain and ear is a reflection of a normal state of homeostasis between the fluid compartments in the brain of cerebrospinal fluid and perilymph-endolymph in the labyrinth of the ear. The normal homeostasis in the structures and contents between the two fluid compartment systems—intracerebral and intralabyrinthine—is controlled by mechanisms involved in the maintenance of normal pressures, water and electrolyte content, and neurotransmitter activities. The initial pathophysiology (a reflection of an alteration in the vascular supply to the brain-ear) is hypothesized to be an initial acute inflammatory response, persistence of which results in ischemia and an irreversible alteration in the involved neural substrates of brain-ear. Clinically, a chronic multisymptom complex becomes manifest. The multisymptom complex, individual for each TBI patient regardless of the diagnostic TBI category (i.e., mild, moderate, or severe), initially reflects processes of inflammation and ischemia which, in brain, result in brain volume loss identified as neurodegeneration and hydrocephalus ex vacuo or an alteration in cerebrospinal fluid production (i.e., pseudotumor cerebri) and, in ear, secondary endolymphatic hydrops with associated cochleovestibular complaints of hearing loss, tinnitus, vertigo, ear blockage, and hyperacusis. The FDVTBE integrates and translates a neurovascular hypothesis for Alzheimer's disease to TBI. This study presents an FDVTBE hypothesis of TBI to explain the clinical association of head trauma (TBI) and central nervous system neurodegeneration with multisensory complaints, highlighted by and focusing on cochleovestibular complaints. A clinical case report, previously published for demonstration of the cerebrovascular medical significance of a particular type of tinnitus, and evidence-based basic science and clinical medicine are cited to provide objective evidence in support and demonstration of the FDVTBE.

Key Words: homeostasis; inflammation; neurodegeneration; neurovascular; traumatic brain injury

Reprint requests: Abraham Shulman, MD, FACS, 450 Clarkson Avenue, Box 1239, Brooklyn, NY 11203. Phone: 718-773-8888; Fax: 718-465-3669; E-mail: metrc@inch.com.

The translation of what is known in basic science of the role of the vascular supply and fluid dynamics of brain and inner-ear fluid systems (i.e., blood-brain barrier/blood-labyrinth barrier [BBB/BLB]), with clinical manifestations in central nervous system (CNS) disease of intracranial hypertension, hydrocephalus, and secondary endolymphatic hydrops (SEH) in inner-ear disease, finds clinical application for the early diagnosis and treatment in all traumatic brain injury (TBI) patients with associated neurodegeneration (ND), as reported in the neurotological evaluation with associated complaints of hearing loss, tinnitus, hyperacusis, and vertigo.

The fluid dynamics vascular theory of brain-inner-ear function (FDVTBE) is hypothesized to provide a framework for integration of the underlying pathophysiology involved in the brain and ear in TBI patients with a diverse and multidimensional clinical symptomatology for improvement in the accuracy of diagnosis and treatment of TBI patients. In our clinical experience with TBI to date, various contributions in the literature are cited in support of the FDVTBE and its clinical translation for TBI diagnosis and treatment of associated complaints of ND, hearing loss, tinnitus, and vertigo.

"Disturbances to inner ear homeostasis can result in cellular toxicity and hearing dysfunction. The blood-labyrinth barrier (BLB) has been characterized and believed to maintain inner ear fluid composition by protecting the inner ear from toxic substances present in the systemic circulation, selectively limiting substance entry into the inner ear" [1].

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. Endolymphatic hydrops (EH) is a byproduct of this process [2].

In general, the BBB is a series of interfaces among arterial blood, cerebrospinal fluid (CSF), and neural tissue that regulate the transport of chemical substances. It controls cerebral homeostasis [3]. The issue of alteration in homeostasis within the fluid compartments of the inner ear or CSF of the 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., local or diffuse EH) secondary to the effects of CSF on the perilymph compartment of the inner ear [4]. Alteration in the fluid dynamics between the brain and inner ear has been demonstrated objectively to be associated with cochleovestibular complaints of hearing loss, tinnitus, vertigo, and ear blockage (EB) alone or in combination [5,6].

"Benign intracranial hypertension (BIH) is a syndrome characterized by increased intracranial pressure (IIP) without focal signs of neurological dysfunction. The diagnosis is essentially made by exclusion of various causes of IIP. The classic presenting symptoms of BIH are headache and/or visual disturbances." Otological manifestations of this syndrome have been described to include head pressure, low-frequency hearing loss, EB, pulsatile tinnitus, and vertigo [7].

"It has been hypothesized that secondary endolymphatic hydrops (SEH) is a factor—not an etiology—influencing the clinical course of tinnitus, particularly of the severe disabling type (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 the brain CSF result in EH and interference in normal function of the inner ear, with resultant inner-ear complaint(s), that can be highlighted by tinnitus rather than by vertigo. The EH may be either localized or diffuse within the cochlear or the vestibular labyrinth (or both)" [3].

The diagnosis of SEH in our clinical neurotological experience since 1972, ongoing and with a focus on subjective idiopathic tinnitus (SIT) since 1979, has been identified and reported to have a significant incidence and to serve as a factor influencing the clinical course of SIT and associated complaints of hearing loss, EB, and vertigo [4].

TBI has been defined by the Centers for Disease Control as "craniocerebral trauma associated with neurological or neuropsychological abnormalities, skull fracture, intracranial lesions, or death. There is a disruption in normal brain function manifested clinically as 'mild' (i.e., a brief change in mental status or consciousness) to 'severe' (i.e., an extended period of unconsciousness or amnesia after the injury)" [8]. A TBI patient may have experienced shock waves from a blast, acceleration-deceleration (collision), or an impact or penetration directly to the skull [9]. The trauma etiology is highlighted by the combined effects of a concussive vibratory sensation and noise on the body, in particular the skull's anatomical structures, and intracranial-intralabyrinthine fluid systems. Symptoms are multiple, and the severity frequently reflects the parameters of duration of exposure, intensity, and frequency of occurrence. Persistence over time may result in chronicity of complaints associated with all categories of TBI.

The diagnostic classification of mild TBI has identified two different mechanisms of injury: blunt or closed-head injury and blast injury. In blunt or closed-head

injury–related mild TBI, the head forcibly strikes another object. In blast injury–related mild TBI, the head is acted upon by a pressure wave (see Hoffer et al., "Blunt and Blast Head Trauma: Different Entities," in this issue). In a mouse model for closed-head injury, molecular changes have been reported, which indicate inflammatory changes [10].

The distinct neuropathological entity of chronic traumatic encephalopathy (CTE) caused by repetitive blows to the head was, in the past, deemed to be a disease seen only in old, retired professional boxers. CTE is an insidious disease beginning with deterioration in concentration, memory, and attention and eventually affecting the pyramidal tract, resulting in disturbed gait, coordination, slurred speech, and tremors [11]. It may apply to the issue of CNS neurodegeneration (CNSND) in the TBI population. The etiology of head trauma has led to multiple diagnostic codes of which TBI is but one, based on the symptomatology that is predominant in the clinical history. Longitudinal studies of TBI patients will establish the relationship, if any, to CTE. The pathophysiological entity of CTE may well reflect a commonality shared among a spectrum of CNS diseases related to the etiology of head trauma.

This publication presents an FDVTBE hypothesis of TBI to explain the clinical association of head trauma (TBI) and CNSND with multisensory complaints, highlighted by and focusing on cochleovestibular complaints. A clinical case report, previously published for demonstration of the cerebrovascular medical significance of a particular type of tinnitus, and evidence-based basic science and clinical medicine are cited to provide objective evidence in support and demonstration of the FDVTBE.

FLUID DYNAMICS VASCULAR THEORY OF BRAIN AND INNER-EAR FUNCTION AND TBI

Hypothesis

It is hypothesized that in all TBI patients with a clinical history of closed or penetrating head injury, the initial head trauma is associated with a vibratory sensation and noise exposure, with resultant alteration in vascular supply to the fluid compartments of the brain and ear (i.e., the FDVTBE). The primary etiology—head trauma—results in an alteration in the local or global vascular supply to the head. Initially, there is a fluctuation, interference, or interaction in the normal fluid dynamics between brain and labyrinth of the inner ear, with a resultant clinical diversity of complaints varying in time of onset and severity. Normal function of the brain and ear is a reflection of a normal state of homeostasis between the brain CSF and the perilymph-endolymph in the labyrinth of the ear.

Normal homeostasis in the structures and contents between the two fluid compartment systems—intracerebral and intralabyrinthine—is controlled by mechanisms involved in the maintenance of normal pressures, water and electrolyte content, and activity of multiple neurotransmitters. The ultimate regulation of the homeostasis of function between the ear and brain are of molecular genetic origin.

The initial pathophysiology, a reflection of an alteration in the vascular supply to the brain-ear, is hypothesized to be an acute inflammatory response accompanied by extra- and intracellular local or diffuse edema in brain and labyrinth, which, over time, results in ND to varying degrees. Persistence of the inflammatory response results in an irreversible alteration in the involved neural substrates of brain-ear, reflected clinically in a chronic multisymptom complex that is individual for each TBI patient, regardless of the diagnostic TBI category (i.e., mild, moderate, or severe). The interference in homeostasis between these two fluid systems of brain-ear (i.e., BBB/BLB), a result of alteration in vascular supply to the brain, is hypothesized to become clinically manifest in the brain by an abnormal alteration-fluctuation in CSF pressure or hydrocephalus (or both) and, in the labyrinth of the inner ear, with a secondary EH. Delay in the identification and treatment of these two factors contributes to chronic inflammation in the ear and brain. The SEH is either primary (i.e., associated with the initial TBI) or secondary (i.e., in response to alteration in CSF pressure). A pathophysiological cascade of events ensues: inflammation, edema, ischemia, and resultant volume loss and ND in neural tissue substrates in the brain and ear. In the brain, the presence or persistence of the intracranial hypertension and accompanying hydrocephalus results in pathological alterations in CNS neuronal tissue and volume loss, highlighted by complaints of interference in cognition and memory. In the ear, the presence or persistence of an SEH results in histopathological alterations in the cochlear and vestibular labyrinths, with cochleovestibular complaints of varying degrees of hearing loss, hyperacusis, tinnitus, vertigo, and EB alone or in combination. The time of onset of the complaints is variable and multifactorial, dependent predominantly on the initial trauma. The clinical course of the complaints is influenced by the anatomy of the ear and brain and antecedent local, systemic, and hereditary factors.

In summary, it is hypothesized that the FDVTBE provides an understanding of TBI and the establishment of a pathophysiology for TBI. The early identification and treatment of the two factors of intracranial hypertension and hydrocephalus in the brain and SEH

in the ear in TBI patients, both initiated by an alteration in vascular supply to the head accompanying head trauma, may interrupt the cascade of events that ultimately can result in clinical symptoms associated with neurodegenerative CNS and inner-ear disease.

Case Report

A case has been reported of a 48-year-old man with the tetrad of complaints that fulfilled the diagnostic categories of Ménière's disease highlighted by EB of fluctuating intensity, occasional tinnitus and vertigo (unsteadiness), and bilateral sensorineural hearing loss, in whom brain magnetic resonance imaging (MRI) results were reported to be negative but nuclear medicine imaging single-photon emission computed tomography (SPECT) identified significant perfusion asymmetries, particularly right-sided and global, compatible with cerebrovascular small-vessel disease. Resultant acetazolamide (Diamox) findings were compatible with multifocal cerebral diaschisis or neuronal loss, predominantly in the right hemisphere. Diaschisis is a neuronal disconnect effect, not a vascular effect. Long-standing vascular effects may result in neuronal loss. Diamox, a diuretic, is also a vasodilator. It provides a test for cerebrovascular insufficiency. A "watershed" effect was demonstrated in the right frontal lobe (i.e., a defect in the most distal part of circulation in major arteries, the arteriolar capillary junction), a characteristic distribution of ischemia. The clinical history of fluctuating hypertension introduced the clinical consideration of a delayed or secondary EH, which in this patient was highlighted by the tinnitus complaint and vertigo. The resistance to medical treatment for the vertigo was hypothesized to have a medical significance that transcended that of only an inner-ear complaint. The EH was clinically considered to be reflective of alteration in the homeostatic mechanisms involved in the fluid compartments of both the ear and brain (i.e., BBB/BLB). Clinically, it was suggested that the medical significance of the tinnitus in the right ear and the balance complaint in this patient was one of cerebrovascular disease that was greater on the right than on the left side with involvement of a delayed or secondary EH of the right inner ear [12].

The SPECT findings suggest that there exists in tinnitus patients a state of central disinhibition over broad cortical levels [3,13–15]. They 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 [12, 15]. In the clinical evaluation of brain perfusion asymmetry with SPECT of brain, one must differentiate between perfusion asymmetries compatible with lack of vascular reserve or neuronal loss [16].

This case report reflects in part our ongoing clinical experiences with tinnitus, which focus on the clinical effects of an initial vascular etiology, resultant pathophysiology, and interference in function in the brain and ear. These experiences are considered to support translation to the FDVTBE for TBI. Specifically, an initial vascular etiology can result in cerebrovascular brain disease with a symptomatology reflective of early-mild TBI. Over time, progression in the initial alteration in vascular supply in the brain and ear is accompanied by pathophysiological processes of inflammation and ischemia, with resultant progressive alteration in the homeostasis of function in the fluid compartments of both: in the brain, an alteration in CSF pressure, secondary hydrocephalus, volume loss, and neurodegenerative disease (NDD) and, in the ear, EH. Clinically, a plethora of complaints become manifest in TBI patients, highlighted in the brain by interference in the functions of cognition and memory and in the ear by cochleovestibular complaints of hearing loss, tinnitus, hyperacusis, and vertigo.

DISCUSSION

Epidemiological support for the association of head trauma (short- and long-term TBI, whether mild, moderate, or severe, with or without a history of loss of consciousness; a commonality of complaints clinically reflective of ND in the ear and brain; and cochleovestibular complaints with local and systemic effects) has been suggested by clinical observations and ongoing patient reports with medical-audiological neurotological evaluation in SIT patients since 1979.

Evidence-based basic science and clinical medicine are submitted in support of the FDVTBE association of ND and cochleovestibular complaints in TBI patients. The reader is referred to the publications for details of the cited reports that follow.

Head Trauma, ND, Cochleovestibular Complaint, and TBI

The association of head trauma with ND in the ear and brain and cochleovestibular complaints were initially reported as clinical neurotological observations in 1991, with a focus on SIT [17]. This association has persisted to date.

CNSND and Tinnitus: Nuclear Medicine Brain Imaging (SPECT) and Fluorodeoxyglucose–Positron Emission Tomography–Computed Tomography

A retrospective review and medical-audiological neurotological analysis of consecutive SIT patients (N = 96) for this association with ND included nuclear medicine

brain imaging (SPECT) and fluorodeoxyglucose–positron emission tomography–computed tomography (FDG/PET/CT) to provide objective data to support this association. Audiological testing revealed a bilateral sensorineural hearing loss of varying degree in all patients. Of these 96 patients, 54 had SIT of a predominantly central type. Nuclear medicine imaging was performed in a selected cohort of 18 SIT patients (18 of 54; ages 39–75 years). ND was reported in multiple neural substrates of the brain obtained with SPECT or FDG/PET/CT of brain. Significantly, the imaging diagnosis of CNSND was associated in the clinical history with cerebrovascular disease in 16 of the 18 SIT patients. Classification of CNSND and tinnitus differentiated between (1) ND of nonspecific or unknown etiology; (2) NDD and ischemia (NDDI) manifested by perfusion asymmetries in the brain associated with ischemia (n = 11 of 18); and (3) CNSND consistent with nuclear medicine criteria for senile dementia of the Alzheimer's type (NDD-SDAT; n = 5 of 18). A medical-audiological profile of patients in whom SIT of the severe disabling type has been clinically suggested to be a "soft" sign of CNSND was identified. The elements of the profile include the patients' neurotological clinical history, physical examination of the head and neck, electrophysiological correlates of cochleovestibular function, spectral analysis of raw quantitative electroencephalography data of brain function, and brain SPECT or FDG/PET/CT imaging. The incidence in a cohort of patients with SIT, ND, NDDI, and NDD-SDAT is expected to vary in different neurotological practices, depending on the demographics and severity of the SIT in the patient population seeking consultation. The occurrence and localization of inflammation and ischemia appear to be random in the CNS. In SIT patients, it involves primarily the neural substrates of the final common pathway (FCP) of tinnitus (frontal, temporal, and medial temporal lobes) [18,19].

The identification of pathological processes of inflammation and ischemia linked to ND in a particular cohort of SIT patients may provide a basis for establishing the medical significance and treatment of SIT and may influence the clinical course of the tinnitus [18]. The nuclear medicine imaging results in this report established a clinical and objective link between neurovascular dysfunction and ND in SIT patients. The clinical application of this report has implications for the diagnosis and treatment of TBI (i.e., the association of complaints of ND and cochleovestibular complaints).

To be considered in the clinical interpretation of the nuclear medicine imaging results in TBI patients is a need to differentiate between the effects of the head trauma on the brain and the associated cochleovestibular complaints. A diversity of TBI neuroimaging results is probable, considering the multiple etiologies and factors associated with TBI (e.g., different types of head trauma, different degrees of noise exposure, different degrees of antecedent sensorineural hearing loss, and possible antecedent cerebrovascular disease). These multifactorial issues for TBI become manifest with brain imaging techniques by the demonstration of different degrees of neuronal activity in multiple regions of interest in the brain, individual for specific brain functions in response to the TBI (e.g., consciousness, perception, attention, affect, memory, cognition, and the aging process). Furthermore, with respect to tinnitus in TBI patients, consider that the clinical type of tinnitus is combined (i.e., cochlear and central types of tinnitus), reflecting combined etiologies of head trauma, noise exposure, and probable cerebrovascular disease.

Fluid Dynamics Vascular Theory of Brain–Inner-ear Function: Hypothesis

The FDVTBE is a clinical translation to TBI of a neurovascular hypothesis for Alzheimer's disease (AD). Interference in cognition and memory in the clinical history is considered to be a consequence of neurovascular dysfunction [20]. Previously, the neurovascular hypothesis for AD was translated for its clinical application to CNSND and tinnitus and provided (1) a basis for challenge to a predominantly sensorineural view of SIT based on the psychophysical and psychoacoustic characteristics of tinnitus to a focus on both the brain and ear reflective of our SIT clinical experience (i.e., the clinical association of SIT with multiple CNS brain functions) [19]; (2) a theory to support our ongoing SIT clinical experience suggesting the medical significance of SIT may be a "soft" sign of CNSND in a special cohort of SIT patients [18]; and (3) a translational theory with implications for both diagnosis and treatment based on a therapy targeting pathophysiological processes of inflammation and ischemia linked to and underlying ND [21]. CNS neurovascular dysfunction may, in a particular cohort of SIT patients, "trigger" (influence) the clinical course of SIT for this special cohort of SIT patients [21].

The proposed neurovascular theory of CNSND and AD includes neurovascular mechanisms of CNSND in a neurovascular unit. A neurovascular unit is conceptualized in the brain to include brain capillaries, pial and intracerebral arteries, and large cerebral arteries in which regulation of local cerebral blood flow molecular transport across the BBB maintains tight control of the chemical composition of the neuronal internal environment. Dysfunction of local cerebral blood flow in the neurovascular unit can result in a reduction in blood supply to the brain, with resultant interferences at the

BBB, cerebrovascular hypoperfusion, and neuronal injury [21].

Common pathways are identified to be a target of inflammation, linked to CNSND. Symptoms of CNSND are hypothesized to be initiated by a vascular etiology and mediated by primary or secondary pathophysiological processes of inflammation and ischemia. Interference in cognition and memory in the clinical history are considered to be a consequence of neurovascular dysfunction with resultant aberrant angiogenesis, senescence in neuronal cells, dysfunction at the level of the neurovascular unit, and hypoperfusion with resultant AD [21].

An interruption in the vascular supply to the head or ear (or both), associated with the etiologies of blunt or blast head trauma injury (local or global in the brain), initially with or secondary to an axonal injury in the ear or the brain, is hypothesized to be fundamental to the FDVTBE in TBI patients. In both the brain and the ear, there is an interruption in the homeostasis of function maintenance. In both, the underlying mechanisms are ongoing, immediate, or delayed in onset for each TBI patient. The brain and ear clinical symptoms may be simultaneous or delayed in onset and are shared or individual between TBI patients. Clinically, in the FDVTBE for TBI, the pathological alterations in the brain are hypothesized to include hemorrhage, edema in multiple neuroanatomical substrates, alteration in CSF pressure, hydrocephalus with resultant brain volume loss and, ultimately, ND, and to be highlighted clinically by interruption in consciousness, perception, attention, affect, memory, cognition, and the aging process. Multiple neural substrates associated with tinnitus, identified via brain SPECT, PET/CT, and FDG/PET/CT, have been hypothesized to be an FCP for tinnitus [19,22].

The FCP is considered to be activated in TBI patients particularly for cochleovestibular complaints. The pathological alterations in the ear may include hemorrhage, dislocation, and histopathological alteration in anatomical structures of the inner ear as cited and SEH, with symptoms of cochleovestibular complaints of sensorineural hearing loss, tinnitus, hyperacusis, EB, and vertigo [1–4].

The mechanisms for ND in TBI, as hypothesized in the FDVTBE, are translated from the neurovascular theory of CNSND and AD [21] and integrated with the clinical experience reported of the association of tinnitus and ND in a selected cohort of SIT patients (i.e., translational neurovascular theory of CNSND and tinnitus) [18,21]. Ultimately, it is hypothesized in the FDVTBE for TBI patients that the association of ND and cochleovestibular complaints is initiated by a vascular etiology and mediated by pathophysiological processes (primary or secondary) of inflammation and ischemia in multiple neural substrates. The cascade of changes associated with ischemia and inflammation are controlled by molecular proteogenomic mechanisms involving glutamate, calcium, and calpain activities [23–25].

Alterations in the neurovascular unit in the brain (i.e., brain capillaries, pial and intracerebral arteries, large cerebral arteries) by ischemia or inflammation (or both) as hypothesized with the FDVTBE when localized in neural substrates can result in NDD (i.e., NDDI and NDD-SDAT). A primary CNS NDD clinically manifest as, for example, AD or frontotemporal degeneration can, by secondary extension or involvement of the FCP, include the symptom of SIT. It has been hypothesized for tinnitus that for NDDI, the primary auditory cortex or associative cortices are primarily involved. For NDD-SDAT, the posterior cortices are primarily involved, with secondary involvement of the primary and secondary associative auditory cortices. What needs to be observed long term is what, if any, is the incidence of transformation of the NDDI and NDD-SDAT to CNS NDD (e.g., AD, frontotemporal degeneration, and Parkinson's disease) [18].

Studies demonstrating alteration in the brain in patients with the TBI diagnosis have been reported using the technologies of MRI, diffusion tensor imaging, quantitative magnetic resonance, SPECT, and magnetic resonance spectroscopy [26].

Long-term MRI, SPECT, and PET/CT brain studies in TBI patients are recommended to identify and correlate structure-function relationships in (1) the clinical course of TBI patients with or without ND and cochleovestibular complaints and (2) the development of clinical manifestations of NDD-SDAT, AD, and frontotemporal degeneration.

Inflammation, Ischemia, and FDVTBE/TBI

The FDVTBE is a translational theory that integrates the pathological processes involved with ischemia and inflammation to explain ND and cochleovestibular complaints in the context of cerebrovascular disease. It is hypothesized for TBI that classic inflammatory disease of the brain is demonstrated in CNSND.

For TBI patients, the evolving SIT clinical experience with nuclear medicine imaging, and neuroscience reports of the interaction and linkage of pathophysiological processes of ischemia and inflammation with ND, are considered to have found clinical significance both for the clinical course of the TBI and modalities of treatment attempting control of the association of complaints of ND and cochleovestibular complaints.

The reports of ischemia and inflammation are clinically considered to be supportive of and the basis for the proposed neurovascular hypothesis of ND for AD. Common pathways link inflammatory and ND diseases.

In primary ND, progressive CNS damage is controlled and promoted by immune mechanisms [27]. It is hypothesized for TBI that classic inflammatory disease of the brain demonstrates ND.

Long-term ischemia, with resultant axonal transport defects, synapse loss, and neuroinflammation, may lead to or accompany future pathological tau-mediated NDD, called *tauopathies* [28]. Pathophysiological processes of ischemia and inflammation have been identified as being involved in CNSND. T-cells and microglia play significant roles in classic neuroinflammatory diseases. The interactions between inflammation and ND are complex. The immune response is significant and includes elements of neuroprotection and cytotoxicity. Microglia activation is a key component of the inflammatory CNS responses [29].

Inflammation is believed to contribute to the progression of AD and to aggravate the outcome after ischemic insult [30]. The initial mechanisms of inflammation are different for stroke and AD (i.e., not primarily vascular but neuronal-axonal in origin, targeting microglia). The inflammatory response in the CNS for autoimmune disease and ND differs from that accompanying stroke (i.e., necrosis), probably through upregulation of heat shock protein production [31]. There may be a significance for both the clinical course of ND and cochleovestibular complaints and treatment based on differences that may exist in TBI patients for the inflammatory response.

The etiology of cerebrovascular disease and the pathophysiological process of ischemia has been clinically identified. Inflammation was hypothesized to be linked to and to precede ischemia, leading to ND [18,21].

Cochleovestibular Complaints and TBI

The clinical identification of different clinical types of tinnitus, one of which is a vestibular-type tinnitus, has clinically established that tinnitus is not a unitary symptom. The association of all clinical types of tinnitus with sensorineural hearing loss is frequent. A vestibular tinnitus was described in 1991 as a clinical type of tinnitus reflecting dysfunction of the vestibular labyrinth. The tinnitus patient may be symptomatic or nonsymptomatic for the symptom of vertigo or other type of balance disorder [14,32].

The clinical contention is that subgroups of vestibular tinnitus, peripheral or central in location, potentially exist [15]. In some patients, the medical significance for the symptom of SIT may be a "soft" sign of gradual progressive cerebrovascular disease and early neuronal loss, with involvement of both the peripheral and central cochleovestibular systems (see Case Report) [12, 13]. The reader is referred to the case report for details.

The incidence and characteristics of auditory dysfunction in blast-related TBI patients (N = 252) admitted to a Department of Veterans Affairs TBI patient unit were examined before and after onset of Operation Iraqi Freedom (OIF). Of TBI patients admitted prior to the onset of OIF, 28% reported hearing loss, and 38% reported tinnitus. Of TBI patients admitted after the onset of OIF, 62% reported hearing loss, and 38% reported tinnitus. The most prevalent type of hearing loss was a sensorineural hearing loss in TBI patients admitted after the onset of OIF [33].

Hearing loss, tinnitus, and hyperacusis are common symptoms reported by patients with TBI. In a study of TBI patients with or without auditory complaints and normal pure-tone audiograms, recording of transient evoked otoacoustic emissions was completed during the presentation of increasing levels of white noise in the contralateral ear. TBI patients with auditory complaints (87%) demonstrated absent or reduced effect of the efferent auditory system as compared to TBI patients without auditory complaints and to normal controls [34].

Vestibular complaints of varying degrees are common in TBI. The clinical identification in TBI patients of the complaint of vertigo of different clinical diagnostic categories and of different clinical manifestations of the complaint of imbalance (see Hoffer et al, "Blunt and Blast Head Trauma: Different Entities," in this issue) is significant. A classification system for posttraumatic balance disorders after mild head trauma has been identified and includes four diagnostic categories: benign positional vertigo, exertional dizziness, migraine-associated dizziness, and spontaneous disorientation [35]. The clinical significance of this study is considered to be the identification of different clinical characteristics of each diagnostic category, which provide a basis for recommendations for treatment and rehabilitation and overlap of injury. The FDVTBE for TBI provides an understanding of the multiple diagnostic categories that reflect the peripheral and central components of the vestibular system. What appears to be evolving for vestibular complaints associated with TBI is an experience considered analogous to what has occurred for tinnitus.

The incidence of the complaint of EB has been reported "as an overwhelming incidence of occurrence" in Ménière's disease, SEH, and a cochlear-type tinnitus [14]. Subjectively, the complaint is indistinguishable by its location (i.e., external, middle, or inner ear). An association of the intensity of the EB and fluctuation in tinnitus intensity is frequent and weaker for sensorineural hearing loss [14]. In TBI patients, it is recommended that the incidence of EB be established in relation to association with complaints of head blockage, sensorineural hearing loss, and headache and with reports of fluctuation of CSF pressure and inner-ear disease,

complaints of which can indicate EB [5], a clinical manifestation of the FDVTEB.

Hyperacusis is an increased sensitivity to sound that occurs with or without hearing loss in SIT patients. Clinically, it is considered an interference in the function of the cochleovestibular system. The results of auditory testing, including loudness discomfort levels, are the basis for the concept of different types of hyperacusis—peripheral, central, or both [36]. In our clinical experience with TBI since 2001, the complaint of hyperacusis has been frequent and may be the predominant complaint. Its most frequent association, when severe, has been with the diagnoses of a predominantly central-type SIT, sensorineural hearing loss, posttraumatic stress disorder, and associated complaints of EB and head pressure.

It has been speculated that the clinical entity of SEH identified in tinnitus patients with vestibular-type tinnitus has medical significance for both treatment and hearing conservation. SEH has been reported in our experience to have an incidence of ± 25–35% [37].

In summary, the cochleovestibular complaints are considered salient features in TBI patients that clinically reflect interference in the homeostasis between the fluid systems and function of the brain and ear as hypothesized in the FDVTBE.

FDVTBE, ND, Hypertension, and TBI

Recent reports of the association among blood pressure, hypertension, and cerebral white-matter lesions provide support for these clinical observations. Specifically, increases and decreases in diastolic blood pressure were associated with more severe periventricular white-matter lesions. Increase in systolic blood pressure was associated with more severe periventricular and subcortical white-matter lesions. Higher ambulatory blood pressure levels and a trend for smaller nocturnal declines in systolic and diastolic levels have been observed to be associated with greater leukoaraiosis [38]. Hypertensive patients with severe periventricular white-matter lucency are more likely to have impaired autoregulation of cerebral blood flow than are hypotensive patients [39].

Significant for the vascular etiology in TBI patients and the clinical course of ND and cochleovestibular complaints as hypothesized in the FDVTBE is the need to identify and treat factors influencing these diagnostic entities, of which hypertension is but one [18,21,32].

Clinical Medical-Audiological Profile of CNSND SIT Patients

A medical-audiological profile of patients in whom SIT of the severe disabling type has been clinically suggested to be a soft sign of CNS NDD has been identified. The elements of the profile include the neurotological clinical history, physical examination of the head and neck, electrophysiological correlates of cochleovestibular function, spectral analysis of raw quantitative electroencephalographic data of brain function, and brain SPECT or FDG/PET/CT. The incidence in a cohort of SIT, ND, NDDI, and NDD-SDAT patients will vary in different neurotological practices, depending on the demographics and severity of the SIT in the patient population seeking consultation [18]. It is recommended that the clinical medical-audiological profile of CNSND SIT patients be identified in all SIT TBI patients in an attempt to establish early diagnosis and treatment of CNS NDD.

Perilymph and Endolymph CSF and the FDVTBE

Alteration in the vascular supply to the head is hypothesized to be associated with initial head trauma in all cases of TBI, with an accompanying alteration in the connectivity of the fluid compartments of both the brain and ear, an interruption in the homeostasis of function between the two, and a resultant clinical symptomatology highlighted by ND in the brain and cochleovestibular complaints in the ear (i.e., the FDVTBE). Support for the anatomical basis for the FDVTBE of this connectivity are the basic science and clinical medicine experiences reported in the publications cited in this section. A connectivity among the fluid compartments of the inner ear, perilymph, and endolymph and the CSF of the brain has long been speculated [40,41].

In cases wherein a perilymphatic fistula (PLF) has been recurrent, lumbar puncture has revealed pseudotumor cerebri or benign intracranial hypertension. Significant tinnitus relief has been accompanied by local closure of the PLF 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 PLF. It has been considered that further improvement can be achieved by cochlear aqueduct blockage or a ventricular peritoneal shunt [42].

Patency of the cochlear aqueduct (CA) in all decades of life has been reported [43]. Although the patency of the CA tends to decline in each decade of life, more than 20% of patients were found to have a patent CA in their sixth decade. The CA patency has been identified and confirmed in all age groups, declining by decades [44].

Support for the association of ear complaints with alterations in homeostatic mechanisms attempting to maintain a normal CSF pressure has been reported based on

the clinical experience of patients with the diagnoses of Ménière's disease and PLF. The two conditions can resemble each other symptomatically and at times are indistinguishable one from the other. In both, the tetrad of complaints associated with Ménière's disease is present. A patent CA has been suspected to be present with a PLF in the round window and oval window or both. CA patency is most likely related to the inner-ear symptoms of hearing loss, balance loss, tinnitus, and ear fullness. Alteration of CSF pressure, by the administration of furosemide (Lasix) or an osmotic diuretic of some other kind or by performing lumbar puncture, with or without a ventricular peritoneal shunt, has been reported to result in both improvement in tinnitus relief and other symptoms of hearing loss and vertigo and increased efficacy for local repair techniques for PLF. Occasionally, performance of a lumbar puncture has revealed a diagnosis of benign intracranial hypertension or pseudotumor cerebri [45].

In summary, it is hypothesized that the CSF may influence the perilymphatic space and perilymph production either by direct communication via the CA (the canaliculi perforantes of the spiral osseous ligament) or by alterations in homeostatic mechanisms influencing the permeability of the BBB/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 EB reported by control of the PLF with and without lumbar puncture and by alteration of CSF pressure support consideration of this hypothesis and its integration into the FDVTBE.

Transcranial cerebral sonography (TCCS) is a noninvasive technique that allows the clinician to detect abnormal intracranial–inner-ear fluid interactions in terms of nanoliter tympanic membrane displacements. The displacements recorded in TCCS are evoked either by the acoustic stapedius reflex or by spontaneous movements generated by intracranial cardiovascular or respiratory pressure waves transmitted through the inner ear to the stapes and thence to the tympanic membrane. The results of the TCCS tests are reported in a series of patients whose diagnoses included PLF and a variety of neurological conditions such as idiopathic intracranial hypertension, Arnold-Chiari type I malformation, sigmoid sinus thrombosis, hydrocephalus, and cerebrovascular malformations. It was concluded that both raised intracranial pressure and abnormal intracranial pressure waves are associated with common neurotological symptoms, including tinnitus, dizziness, and hearing dysfunction (see Lehrer et al., "The Value of Transcranial Cerebral Sonography in Diagnosing Neurootological Disorders," in this issue). This article is a significant contribution for an increasing literature supporting the hypothesis of the connectivity between the fluid compartments of the brain and ear and support for the anatomical basis for the FDVTBE.

SEH: Temporal Bone Histopathological Evidence of EH Without Ménière's Disease

It has been speculated that the clinical entity of SEH identified in tinnitus patients with vestibular-type tinnitus has a medical significance for both treatment and hearing conservation, as seen in a case report of the temporal bone findings of a female patient who died at age 96. In her childhood, a hearing loss was reported after an ear infection. At age 67, "a nonfluctuating sensorineural hearing loss of the right ear averaging 57 dB, with an ascending configuration" was recorded [46]. "Electronystagmography revealed a 67% reduced vestibular response on the right side. No spontaneous nystagmus. Some dysequilibrium was reported later in life presumed to be due to reduced function in the right labyrinth" [46]. In 1977, the patient reported vertigo, ear pressure, and tinnitus in the right ear [47]. At age 96, audiometric testing reported a "slight progression of hearing bilaterally, consistent with presbycusis. Histopathology of the rt temporal bone revealed 'extensive hydrops'"; the endolymphatic duct was obstructed by new bone. The temporal bone findings in the left ear "were essentially normal for the patient's age" [46].

The temporal bone histopathological evidence of endolymphatic hydrops (EH) without Ménière's disease is clinically considered histopathological evidence of an SEH, presumed to have been present prior to age 67. The issue of alteration in homeostasis within the fluid compartments of the inner ear or CSF of the 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. local or diffuse EH) secondary to the effects of CSF on the perilymph compartment of the inner ear [4].

We consider that although no single theory has been posited that adequately defines the role of the BLB or BBB (or both) in the development of inner-ear pathological processes, the results of basic science experiments and histopathological examination with the electron microscope and the reported morphological changes in inner-ear structures, combined with our clinical experience with SIT, is clinically considered to support this association [3].

The APOE4 Gene, the FDVTBE, and TBI

The APOE4 gene has been investigated for its association with AD [48]. A significant association of the

APOE4 gene with a poor outcome of TBI 6 months after injury—but not with the initial severity of brain injury—has been reported [49]. This meta-analysis is considered potentially significant for the FDVTBE and its clinical application for diagnosis and treatment of ND in the TBI population.

CONCLUSIONS

The FDVTBE is presented as a framework for understanding the clinical course of development of the pathophysiology of head trauma in the brain and ear, presumed to be initially vascular, highlighted by a symptomatology of CNSND, multisensory disorders, and cochleovestibular complaints in patients with diagnosed TBI. The FDVTBE is a translation of a neurovascular theory for AD for TBI and its association with ND and cochleovestibular disorders of hearing loss, tinnitus, and vertigo.

The FDVTBE postulates that alterations in homeostatic neurovascular mechanisms in the fluid compartments of the brain and ear attempting to maintain normal function are reflected initially in alterations in CSF pressure in the brain and development of EH in the ear. Evidence-based basic science and clinical medicine have been presented in support of the FDVTBE and TBI. The FDVTBE has implications for TBI diagnosis and treatment of ND and cochleovestibular disorders of hearing loss, tinnitus, hyperacusis, and vertigo, with resultant hearing conservation, tinnitus relief, and vertigo control.

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