Postural stability:
Effects of cochlear-implant surgery, auditory inputs and mitochondrial genetics

Iman Ibrahim, MD, PhD

Department of Otolaryngology – Head & Neck Surgery
McGill University, Montreal, Canada
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Contents

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Preface

This thesis comprises 3 manuscripts. The first manuscript (Effect of Cochlear Implant Surgery on Vestibular Function: Meta-analysis study) is found in Chapter 2. The second manuscript (Assessment of auditory input in normal hearing individuals and hearing aid users) is found in Chapter 3. The third manuscript (Mitochondrial mutations associated with hearing and balance disorders) is found in Chapter 4.

Contribution of Authors

Authors: Anthony Zeitouni (AZ), Sabrina Daniela da Silva (SDS), Iman Ibrahim (II), Mev Domiguez (MD), Bernard Segal (BS).

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Abstract

Background: Dizziness is the most common complaint of patients over 65 who consult a physician. Falls have been identified as a leading cause of mortality in the USA after highway accidents. Twenty percent of nonfatal cases involving days away from work was caused by fall related incidents. The interaction between hearing and balance problems is evident in cases of cochlear implant surgery, where some patients either suffer from balance problems before the surgery, or complain from balance issues after the surgery. Age-related hearing loss is a gradual and progressive deterioration of cochlear hair cells function, causing a progressive auditory deficiency in adults. It occurs in 25 to 40% of those aged 65 year or older, in 40 to 66% of those aged 75 or older, and in 80% of those above 85. Despite the anatomical proximity and the similarities in structure and function between The organ of hearing (the cochlea) and the organs of balance (the Utricle, the Saccule, and the three Semicircular Canals), the interactions between auditory information and the maintenance of postural balance have not been widely studied.

The term “spatial hearing” refers to the ability to localize sound sources, taking advantage of the temporal and spectral differences between the acoustic signals reaching both ears. Spatial hearing enables listeners to detect sounds in challenging acoustic conditions.

Considerable research has been done to better understand the various causes of hearing loss (e.g. heritability, environmental factors, medical conditions, ototoxic agents, etc.). However, many underlying molecular mechanisms have not yet been clearly identified. For example, it is known that DNA damage and reduction in mitochondrial function can contribute to hearing loss by causing alterations in vascular plasticity, increasing vascular permeability, genetic mutations and by increasing production of reactive oxygen species (ROS).

Objectives: This thesis aimed: 1) to conduct a literature review on the possible interaction(s) between hearing and balance. 2) to evaluate effects of cochlear-implant surgery on postural stability and vestibular function, 3) to determine whether providing an auditory input results in improved postural stability in both normal subjects and hearing aid users, characterizing the effect of this auditory input on postural stability and 4) to conduct a literature review to investigate mitochondrial DNA mutations/deletions and their possible association with hearing and balance disorders.

Results: First, **c**ochlear-implant surgery significantly affected the results of caloric and VEMP testing. However, HIT results, posturography, and DHI, scores were not significantly affected after CI surgery. Second, examining the effect of auditory input on postural stability showed that normal balance performance was not affected by the absence of auditory input, while hearing impaired individuals' postual performance was worsened during earplug insertion particularly during Romberg testing (decrease was not significant). Hearing aïd users had a significantly better postural performance with hearing aids on (P = 0.012 for Romberg test, and P = 0.011 for Tandem test). For sound localization performance: Hearing impaired individuals had significantly lower correct localization scores compared to normal hearing individuals (P = 0.046.) Hearing aid users performed better with their hearing aids on, however, this improvement was not significant.

Conclusions: Overall, the clinical effect of CI surgery on the vestibular function was found to be insignificant. Nonetheless, the potential effects of surgery on the vestibular system should be discussed with CI candidates before surgery. Although auditory input does not seem to have an effect on postural stability in normal hearing individuals, hearing impaired individuals and hearing aid users had a significant improvement in their postural stability in the presence of auditory input.

Résumé

Introduction : Le vertige est la plainte la plus courante, selon laquelle les patients de plus de 65 ans consultent un médecin. Les chutes ont été identifiées comme la deuxième raison de mortalité la plus fréquente aux États-Unis après les accidents de la route. Vingt pour cent des cas non mortels impliquant des jours loin du travail ont été causés par des incidents liés aux chutes. L'interaction entre les problèmes d'audition et d'équilibre est évidente dans les cas de chirurgie d'implant cochléaire. Certains patients souffrent de problèmes d'équilibre avant la chirurgie ou se plaignent des problèmes d'équilibre après la chirurgie. La perte d'audition liée à l'âge est une détérioration graduelle et progressive de la fonction des cellules cochléaires, entraînant une déficience auditive progressive chez les adultes. Cette perte auditive se trouve parmi 25 à 40% de ceux âgés de 65 ans et plus, parmi 40 à 66% de ceux âgés de 75 ans ou plus et parmi 80% de ceux de plus de 85 ans. Malgré la proximité anatomique et les similitudes de structure et de fonction entre l'organe De l'ouïe (la cochlée) et des organes de l'équilibre (l'utricule, le saccule et les trois canaux semi-circulaires), les interactions entre les entrées auditives et le maintien de l'équilibre postural n'ont pas été largement étudiées.

Le terme “audition spatiale” fait référence à la possibilité de localiser les sources sonores, en profitant des différences temporelles et spectrales entre les signaux acoustiques atteignant les deux oreilles. L'audition spatiale permet aux auditeurs de détecter des sons dans les conditions acoustiques difficiles.

Des études considérables ont été faites pour mieux comprendre les différentes causes de la perte d'audition (par exemple, l'héritabilité, les facteurs environnementaux, les conditions médicales, les agents ototoxiques, etc.). Cependant, de nombreux mécanismes moléculaires sous-jacents n'ont pas encore été clairement identifiés. Par exemple, on sait que les lésions de l'ADN et la réduction de la fonction mitochondriale peuvent contribuer à la perte d'audition en provoquant des altérations de la plasticité vasculaire, l'augmentation de la perméabilité vasculaire, des mutations génétiques et l'augmentation de la production d'espèces réactives d'oxygène (ROS).

Objectif: Le but de ce travail est: 1) effectuer une revue de la littérature sur les interactions possibles entre l'audition et l'équilibre. 2) effectuer une méta-analyse pour étudier les effets

Possibles de la chirurgie d'implant cochléaire sur la stabilité posturale. 3) déterminer si la fourniture d'une entrée auditive avec une fréquence spécifique (1/3 d'octave de bruit avec une fréquence centrale de ~ 3 kHz) entraînera une amélioration de la stabilité posturale chez les utilisateurs d'aides auditives et pour caractériser l'effet de cette entrée auditive Sur la stabilité posturale. 4) effectuer une revue de la littérature pour enquêter sur les mutations / délétions de l'ADN mitochondrial et leur lien avec les troubles de l'ouïe et de l'équilibre.

Résultats : Étude de méta-analyse : la chirurgie de CI a significativement affecté les résultats des tests caloriques et VEMP. Cependant, les résultats HIT, posturographie et DHI, les scores n'ont pas été significativement affectés après la chirurgie CI. Étude prospective de cas-témoins : le rendement normal des équilibres des individus n'a pas été affecté par l'absence d'apport auditif (insertion d'un bouchon d'oreille), alors que la performance des personnes malentendantes a diminué avec l'insertion des bouchons d'oreille, en particulier dans le test de Romberg, mais cette diminution n'a pas été significative. L'audition des utilisateurs d'aides auditives avait une meilleure performance avec les prothèses auditives, et cette amélioration était significative (P = 0.012 pour Romberg, et P = 0.011 pour Tandem). Pour la performance de la localisation du son : les personnes ayant une déficience auditive affichent des scores de localisation correcte nettement inférieurs à ceux de l'audition normale : P = 0,046. Les utilisateurs de l'aide auditive ont mieux réalisé avec leurs prothèses auditives, mais cette amélioration n'a pas été significative.

Conclusions : Dans l'ensemble, l'effet clinique de la chirurgie d'implant cochléairesur sur la fonction vestibulaire a été jugé négligeable. Néanmoins, les effets potentiels de la chirurgie sur le système vestibulaire devraient être discutés avec les candidats d'implant cochléaireavant l'intervention chirurgicale. Bien que l'apport auditif ne semble pas avoir d'effet sur la stabilité posturale chez les personnes ayant une déficience normale, les personnes ayant une déficience auditive et les utilisateurs d'appareils auditifs semblent avoir une amélioration significative de leur stabilité posturale en présence des entrées auditives.

Disclosures

The investigators do not have any conflicts of interest to declare.

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List of Abbreviations

ADP: Adenosine diphosphate

ATP: Adenosine triphosphate

CE: Capillary electrophoresis.

CI: Cochlear Implant

CNS: Central nervous system

Cyt c: Cytochrome c

dB: deciBel

DCN: Dorsal cochlear nucleous

DHI: Dizziness Handicap Inventory

DNA: Deoxyribonucleic acid

H_2O_2: Hydrogen peroxide

HIT: Head Impulse Test

IC: Inferior Colliculus

KHz: Kilo Hertz

LSO: Lateral superior olive

MD: Mean Difference

MSO: Medial superior Olive

mtDNA: mitochondrial deoxyribonucleic acid

NO: Nitric oxide

OXPHOS: Oxidative phosphorylation

RR: Relative Risk

SC: Superior colliculus

SCCD: Superior semicircular canal dehiscence

SOT: Sensory Organization Test

VEMP: Vestibular Evoked Myogenic Potential

Chapter one: Introduction: Contribution of Auditory Input to Postural Stability in Hearing Aid Users

1.1. Literature Review

The hearing organ (the cochlea) and the vestibular organs (the semi-circular canals, utricle and saccule) share the same origin (the otic vesicle), where the cochlear duct and saccule arise from the ventral part of the vesicle, and the utricle, semicircular canals, and endolymphatic duct arise from the dorsal part of the otic vesicle. Because of that shared embryological origin, both organs lie in anatomical proximity, within the inner ear cavity [1].

Similarities in the mechanism of stimulation of both organs is also observed. Auditory transduction is the main function of the cochlea. The acoustic stimulus is the sound pressure waves that propagate in a medium (usually the air). The tympanic membrane is very sensitive to these pressure waves, and it vibrates back and forth, transmitting the movement to the middle ear ossicles, and hence to the cochlea through footplate of stapes, which moves in and out like a piston, transmitting the movement to the oval window. This movement leads to stimulation of the sensory cells, which are mechanoreceptors, known as the hair cells, located in the hearing sense organ (organ of corti), inside the cochlea. By stimulating the hair cells, an action potential is generated, and transmitted via the cochlear nerve fibers to the central nervous system. The cochlea converts the acoustic waveform into electrochemical impulses that can be transmitted to the central nervous system (CNS). During this sensory transduction process, the cochlea effectively analyzes a sound stimulus in terms of its frequency, intensity, and temporal properties. This information is further processed and interpreted at the higher centers in the CNS.

On the other hand, the vestibular labyrinth is the main organ of equilibrium. It plays a major role in maintaining postural stability and spatial orientation. Vestibular input to areas of the nervous system involved in eye movement and motor control help stabilizing the image of a fixed object on the retina during head movement, and help adjusting muscle activities to maintain a stable upright posture, respectively.

Similarly, the sensory cells located inside each of the five organs, are mechanoreceptors, known also as the hair cells. The sensory organ in which those hair cells are located either in the cristae

of the semicircular canals, or in the maculae of the utricle and saccule. The hairs of hair cells are embedded in a gelatinous mass (the cupula), or in the otolithitic membrane, in the semicircular canals or in the utricle and saccule, respectively. During movement, fluid inertia results in displacement of the gelatinous membrane, and bending of the hair cells. This eventually leads to stimulation of the hair cells and generates action potentials [2].

From the above, we see that both the cochlea and the vestibular labyrinth have mechanoreceptors that respond to movement.

1.1.1 Embryology of the inner ear

Because of its complicated and irregular shape, the inner ear is known as the labyrinth. It starts to develop 3 weeks after fertilization, before the middle and external ears. The labyrinth begins as an ectodermal thickening called otic placodes, which appear on either sides of the hindbrain (rhombencephalon). Otic placodes invaginate to form the otic pits. These otic pits then pinch off from the surface to form a fluid-filled sac, surrounded by epithelium (the otic vesicles, or otocycts), within the mesenchyme of the head. Some of the head mesenchyme closely surrounds the otocyst, forming what is known as the otic capsule. Later during fetal maturation, the otocyst will develop to become the structures that form the membranous labyrinth of the internal ear. Mesenchyme around the otocyst will develop to form the cartilage that later ossifies to form the bony labyrinth. The fluid that fills the membranous labyrinth is called the endolymph, which is an intracellular fluid, rich in potassium, unlike the perilymph, which is an extracellular fluid, rich in sodium (hence it is negative compared to the endolymph), and fills the space between the bony and membranous labyrinth [3].

To summarize, the inner ear, aka the labyrinth, is a continuous membranous cavity, filled with endolymph, surrounded by perilymph, and enclosed within the bony labyrinth, which is enclosed within the petrous part of temporal bone.

1.1.2 Interactions between auditory and vestibular function

Several physiological and pathological phenomena exist, where auditory stimulation can result in a vestibular response, some of these phenomena are discussed below.

The Tullio phenomenon (named after Pietro Tullio, an Italian physiologist who first reported the phenomenon in a variety of animals), refers to recurrent osscillopsia or disequilibrium in response to loud sounds or middle ear pressure changes, as in the Valsalva maneuver. Many patients who experience Tullio phenomenon have superior semicircular canal dehiscence (SCCD). Studies revealed that oscillopsia and/or disequilibrium occur as a result of superior semicircular canal stimulation [4].

Patients with pathological fistulae, and individuals working in extremely noisy environments, such as engineers working in the development of jet engines, also experience disequilibrium or oscillopsia with loud sounds.

Dieterich et al. (1989) [5] attributed Tullio phenomenon to a hypermobile stapes. Minor et al. (1998) [6] reported abnormalities of the vestibular-ocular and vestibular-spinal responses and abnormalities of auditory function associated with Tullio presentation. The labyrinth has two mobile windows: the oval window, on which, the footplate of stapes ossicle exerts piston-like motion to transmit sound pressure waves, and the round window, which moves outward in response to the inward movement of the stapes footplate. It is thought that bone defect (dehiscence) over the superior canal creates a third mobile window in the labyrinth that transmits low frequency sound energy through the labyrinth. Sounds cause endolymph flow in the superior canal, resulting in the vestibular reaction. Superior canal dehiscence could result from a developmental abnormality, a trauma to the temporal bone, or may result from thinning of bone as a result of aging [7].

Vestibular evoked myogenic potentials (VEMP) are an example of a physiological phenomenon where auditory stimulus leads to a vestibular evoked response. VEMP Is performed to test the saccule and the inferior vestibular nerve function. The saccule, which is the lower of the two otolithic organs, retains some sound sensitivity that can be measured. It is thought that this sensitivity is a remnant from the saccule's use as an organ of hearing in lower animals [2, 8].

Sound stimulates the vestibular apparatus, particularly the saccule [9], and this stimulation is conveyed through the vestibular nerve and ganglion to the medulla, where the vestibular nuclei are located. Impulses from the brainstem stimulate neck muscles (esp. Strenocleidomastoid muscle), via the medial vestibulospinal tract (MVST).

Vestibular symptoms are common following Cochlear Implant (CI) surgery. Almost one third of CI patients are affected, with various onset, severity and course of vertiginous episodes. Tullio phenomenon occur in some CI patients, where dizziness, nystagmus, and vestibulospinal disorders occur during operation hours of speech processor, and has been attributed mostly to electrical stimulation of the vestibular labyrinth. However, other cases of postoperative vertigo occur immediately postoperatively, before activation of the speech processor. Several pathophysiological mechanisms for postoperative vertigo in CI patients have been suggested, such as direct trauma to vestibular labyrinth structures, and labyrinthitis [10].

Vestibular input – on the other hand - helps CNS interpret sound localization cues properly. We are able to localize horizontal sound sources direction, because our auditory system analyzes the intensity and timing differences between the auditory signals that reach each ear. Vertical sound locations are determined monaurally through direction-dependent pinna reflections, which also help distinguishing front from back sound source locations [11, 12]. When we move or turn our heads, these intensity and timing cues are altered. This is supposed to distort the perception of the sound source, but we perceive a stable sound source in reality, because CNS interprets auditory signals in reference to signals of head movement. The vestibular system is crucial for providing theseinformation. Sound localization cues (interaural intensity and timing differences), are processed in the lateral and medial superior olivary nuclei (LSO & MSO), respectively. While the spectral-shape cues are processed in the dorsal cochlear nucleus (DCN). The output of the superior olivary nucleus travels via the lateral lemniscus to the inferior colliculus (IC). The superior colliculus (SC), where visual input is processed, has efferent projection to the IC, and it is suggested that both IC and SC serve as integration areas for visual and auditory input [13].

A physiological phenomenon called “auditory illusion”, describes why blindfolded listeners would perceive a stationary sound as a moving sound, in a direction opposite to their movement, when they are rotated around a vertical axis. When sound localization cues are distorted during vestibular stimulation, a shift in subjective body position occurs [14].

1.1.3 Factors controlling postural stability

Postural stability refers to the ability of the person to control the body's center of gravity within a given base of support (usually both feet). Static postural stability refers to the ability of a person to maintain balance in static conditions. Another form of postural stability, is dynamic postural stability, which refers to the person's ability to maintain balance during transition from a dynamic to a static condition. Both types of postural stability require complex coordination of central processing of sensory input from visual, vestibular, and somatosensory pathways, as well as the resultant efferent response. Here, I will be discussing static postural stability and factors affecting it.

The integration and regulation of sensory inputs required to maintain balance occurs seamlessly in the CNS, which selects to increases the activity of the sensory channel that provides most useful information, and decrease or neglect the activities of another sensory channel at a given point of time, in order to maintain and/or regulate body balance. Although multisensory feedback is essential for postural control, individuals differentially depend on combinations of somatosensory, vestibular, and visual feedback for postural stability.

The dominant dependence can change with circumstance, including impairment of one or more of the senses [15]. Partial compensation occurs in these systems to ensure balance not only for major impairment, but also for temporary interruptions, such as when we close our eyes. In this situation, sway variability increases, but balance can be maintained. Healthy young individuals have the greatest Postural stability, because of their intact sensory organs and robust compensation mechanisms [16, 17].

Horak (2006) [18] quantified the relative contribution of each sensory system to postural stability. According to Horak, maintaining balance depends largely on somatosensory information (70%), followed by vestibular input (20%), and finally visual input (10%).

Maintaining postural stability is a complex process, that requires intact sensory systems, central processing of various sensory inputs, sending efferent signals back to sensory systems and musculoskeletal system, and an intact musculoskeletal system to execute the required motor action. (Shaffer & Harrison, 2007).

Impairment or disturbance of one of the sensory inputs is compensated for by increasing the contribution from the remaining intact systems, to maintain postural stability [19].

1.1.3.1 Effect of vision disorders on postural stability

Visual input is crucial for postural stability. This fact can readily be recognized, as normal healthy individuals attempt to maintain their balance with eyes closed, as opposed to maintaining balance with eyes opened [20]. Several studies investigated the contribution of the visual system to postural stability, particularly the effect of distorted vision on balance. Patients with visual problems typically depend more on the vestibular and somatosensory systems to compensate for the decreased or distorted visual input. Visual contribution becomes particularly important when proprioceptive input is lost. Dornan et al. (1978) [21] reported that above-knee amputees depend on visual input for their static balance maintenance.

Given the importance of visual input to maintaining balance, it can be expected that distorted visual input can result in postural instability. Gantchev et al. (1981) [22] found that a delayed visual feedback could increase and postural instability and body sway. Along with these findings, moving visual scenes were found to increase sway in the same direction of movement [23, 24]. Anand et al. (2003) [25] reported that cataractous and refractive blur decrease postural stability.

1.1.3.2 Role of vestibular system in maintaining postural stability

The vestibular system has a unique character; as soon as vestibular input reaches the CNS centers, it integrates with inputs from other sensory modalities, leading to a multisensory or multimodal response. This explains why it is difficult to measure a "pure" vestibular response. However, vestibular input is crucial for several CNS functions with variable complexities [26].

Among CNS functions that depend on vestibular input are postural reflexes, that serve to maintain an upright posture. The vestibular apparatus sends sensory afferents for postural reflexes, while the efferent responses are directed to the skeletal muscles [27]. Movements of the neck and/or limbs stimulate the vestibular system, and this initiates vestibulo-collic and vestibulo-spinal reflexes, respectively.

The vestibular nuclei are grouped in the medulla oblongata and the pons. These nuclei, together with reticular nuclei in the pons, send excitatory signals to the antigravity muscles via the lateral and medial vestibulospinal tract [27].

1.1.3.3 Role of proprioception in maintaining postural stability

Normal individuals rely mainly on proprioceptive and cutaneous inputs to maintain balance, and perform the majority of daily living activities. Proprioception and cutaneous sensations convey information about spatial and mechanical status to the musculoskeletal framework. The CNS interprets movements of the body in reference to a static reference, such as walls. The muscle spindles and Golgi Tendon Organs are the mechanoreceptors responsible for conveying information about the muscle's length, velocity of contraction, and tensile forces [28].

Antigravity muscles include: Soleus, Gastrocnemius, Tibialis Anterior, Gluteus Medius, Tensor Fascia Lata, Iliopsoas, Thoracic Erector Spinae, and Abdominals [29].

In addition to the contribution of different individual senses to the complex process of postural stability, interactions between each sensory input and the other were reported, such as interactions between visual and vestibular inputs, vision and neck proprioception, vision and lower limb proprioception, visual and auditory input, vestibular and neck proprioception, and vestibular and lower limb proprioception [13].

1.1.4. Research investigating auditory contribution to postural control

Despite the close anatomical location between the hearing and balance organs, and physiological similarities in both organs' receptor function, few studies have investigated the potential contribution of auditory input to postural stability.

Humans can detect sounds in the frequency range 20Hz to 20,000Hz. Auditory sensory hair cells transform vibrational energy into electrical signals. Information passes along the auditory nerve and terminates in the dorsal and ventral cochlear nuclei. Ascending to the auditory cortex, the information is transmitted via the lateral lemniscus to the inferior colliculus, then to the medial geniculate nucleus, and finally to the primary auditory cortex via the auditory radiation [30].

Juntunen et al. (1987) [16] and Kilburn et al. (1992) [31] reported that individuals with hearing loss showed postural instability. They concluded that the auditory system could have an impact on postural control. Juntunen et al. (1987) [16] suggested that impulse-noise induced hearing loss can result in subclinical damage to the vestibular system.

Rumalla et al (2015) [32] tested balance function in older adults who use hearing aids, using the Romberg on foam and the tandem stance tests, with and without hearing aid activation, in the presence of a stationary sound source during hearing aid activation. They found a significant improvement in both tests, and a decrease in fall risk with the use of hearing aids. They argued that these results improve our understanding of balance mechanisms, where auditory cues could be important for maintaining balance, and hence, hearing aids could be a prevention and/or treatment modality for postural instability. Another study by Easton et al. (1998) [33] tested postural sway in sighted (but blindfolded), and congenitally blind people, using two fixed sound sources (speakers), adjacent to each ear. It was found the presence of auditory input reduced movement of the center of gravity compared to standing in silence. Kanegaonkar et al. (2012) [34] also found a significant contribution of auditory input to postural stability in normal subjects, as revealed by improvement in sway on a Nintendo Wii platform.

Juntunen et al. (1987) [16], Raper & Soames (1991) [35] Kilbum et al. (1992) [31], Soames & Raper (1992) [36], and Sakellari & Soames (1996) [37] found that auditory input could influence balance. Hiengkaew (2000) [13] conducted several studies on different sensory modalities-combinations. They concluded that both individual and interactive effects of visual, vestibular, proprioceptive and auditory inputs all influenced postural control.

Sakellaki & Soames (1996) [37] suggested that sound frequency could affect anteroposterior body sway, while sound intensity could affect mediolateral body sways. They also reported that the effect of sound on postural control appears to vary according to the sound frequency. While certain frequencies could have a stabilizing effect (such as 346 Hz and 842 Hz), others, could have a destabilizing effect (45 Hz and 842 Hz).

1.1.5. Research investigating the effects of cochlear implant surgery on postural stability

The interaction between hearing loss and balance problems is evident in cochlear implant surgery candidates and patients. Some cochlear implant candidates suffer from balance problems, as reported by both subjective and objective tests, and some suffer from balance problems after the surgery [38, 39, 40]. Cochlear implant (CI) surgery is the standard procedure for the treatment of hearing loss for cases where hearing aids are no longer useful or sufficient, cochlear. CI attempts to replace the function of hair cells that are no longer able to stimulate primary auditory neurons in response to sound. While the effects of CI surgery on residual cochlear function is well studied, less attention has been given to its effects on vestibular function. Such effects occur because CI surgery frequently affects the vestibular apparatus, which is in close anatomical proximity to the auditory system.

Various mechanisms that could lead to vestibular dysfunction during or after CI surgery have been suggested: 1) direct trauma caused by electrode insertion, 2) acute serous labyrinthitis due to cochleostomy, 3) foreign body reaction with labyrinthitis, 4) endolymphatic hydrops, and 5) electrical stimulation from the implant itself [10].

Vestibular dysfunction following CI surgery can be assessed by a wide variety of tests, such as the bi-thermal caloric test and the vestibular-evoked-myogenic-potential (VEMP) test [10, 38-42]. However, not all CI recipients suffer from postoperative dizziness [10, 38-41], and CI recipients reported different forms of dizziness after surgery. Postoperative dizziness had different characteristics, onset, and duration [42].

Due to the increasing use of bilateral implantation, it is important to be able to quantify the effects of CI surgery on the vestibular system. The results of such a study would benefit both the CI team and patients. Thus there is a need for a study to evaluate the effects of CI surgery on vestibular function and postural stability in adult patients having sensorineural hearing loss (SNHL) who underwent unilateral or bilateral implantation.

1.1.6. Research investigating Mitochondrial mechanisms that contribute to deterioration of both auditory and vestibular function

Mitochondria are frequently described as the "power plant" of the cell. They are responsible for many function, only three of the most important function of the mitochondria will be discussed here. The first function is the generation of Adenosine triphosphate (ATP), by catalyzing the phosphorylation of cellular adenosine diphosphate (ADP) to produce ATP and supply energy. Along with approximately 60 nuclear encoded proteins, the 13 mitochondrial proteins form the five enzyme complexes of the respiratory complex required for Oxidative phosphorylation (OXPHOS): complex I reduced nicotinamide adenine dinucleotide dehydrogenase, complex II, complex III cytochrome c oxidoreductase, complex IV cytochrome c oxidase, and complex V ATP synthetase [43].

The second function, is to control reactive oxygen species (ROS), and maintain cellular redox homeostasis, which is the continuously challenged oxidative/nucleophilic balance. ROS are reactive derivatives of O2 metabolism, including superoxide anion (O−2), hydrogen peroxide (H_2O_2), and nitric oxide (NO).

Finally, mitochondria play an important role in programmed cell death (aka apoptosis). The core process in apoptosis is the activation of caspases which ae a group of cysteine proteases that can cleave cellular substrates to dismantle cell contents. Apoptosis has two pathways, extrinsic & intrinsic. The intrinsic pathway is also known as the mitochondrial pathway, because of the essential involvement of mitochondria, which acts as the site where antiapoptotic and proapoptotic proteins interact and determine cell fates, and is also the origin of signals that initiate the activation of caspases through various mechanisms. For example, cytochrome c (Cyt c) is a key component of the apoptosome complex for activation of the initiator caspase-9. [43, 44].

There are two copies of the genetic origin of respiratory enzymes, in the nuclear DNA and in the mitochondrial DNA (mtDNA). Therefore, a respiratory chain deficiency can theoretically give rise to a wide spectrum of symptom in different organs and tissues, including the sensory systems, such as hearing loss, with different modes of inheritance, and it can be manifest at any age. This fact makes it difficult to diagnose a respiratory chain deficiency, when only one abnormal symptom is present. However, when two or more unrelated symptoms are observed, it

becomes easier to consider respiratory chain deficiency. Unfortunately, currently available treatments, which depend mainly on dietary modifications, do not significantly influence the deteriorating course of the disease.

Under basic metabolic conditions, the mitochondrial antioxidant machinery can maintain redox homeostasis (the steady state between oxidative and reductive Forces). However, if there is an excess production of ROS, oxidative stress occurs and this can affect various organelles and pathways in the cell, ultimately leading to apoptosis or other forms of cell death.

Oxidative stress, which is defined as the failure to maintain redox homeostasis permitting cell death pathways to proceed, is associated with several forms of disease as well as the aging process. It is usually associated with the aging process, as well as several other pathogenic processes in several diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis ROS may also affect the mitochondrial membrane potential and energy metabolism, leading to damage of mitochondria themselves [45, 46].

Stria vascularis are responsible for establishing the endocochlear potential and the driving force for transduction, and that explained why stria vascularis has the highest metabolic rate of all inner ear structures, as confirmed by early studies [47, 48]. Compared to stria vascularis, hair cells have a rather low metabolic rate, that is also lower than that of supporting cells based on histochemical studies of enzymes involved in energy metabolism [49]. However, their metabolism is still primarily aerobic [50] hence, mitochondria is essential for their fate as much as other cell types. Outer hair cells are more susceptible to oxidative stress due to a lower content of antioxidants [51].

As mentioned above, oxidative stress is a process that occurs in aging as well as several pathological processes including the pathology of acquired hearing loss. Several reviews addressed ROS-based and other mechanisms of toxicity in drug-induced, noise-induced, and age-related hearing loss (aka. Presbyacusis) [52 -55].

In animal models of hearing loss, the co-administration of antioxidants effectively prevents or attenuates morphological and functional drug- and noise-induced hearing loss [56].

mtDNA is frequently undergoing replication independent of the cell cycle, and is particularly sensitive to damage from oxidation due to the lack of protective histones. mtDNA mutations accumulate and expand with age, contributing to age-related diseases. Some age-related conditions are epidemiologically linked with hearing loss. A meta-analysis suggests that higher prevalence of hearing loss is in diabetic patients, regardless of age [57].

Comparative post-mortem temporal bone analysis showed increased mtDNA deletions and mutations in cochlear tissues, in individuals who had presbyacusis compared to normal individuals (mean common deletion level of 32 ± 14 % in the presbyacusis group, compared to 12 ± 2 % from a normal hearing age-matched group). A significant correlation was established between the common deletion level in the cochlear tissue and the severity of hearing loss [58].

Presbyacusis is a common age-related process in mammals, and is correlated with age-related accumulation of mtDNA deletions and/or mutations in cochlear tissue. Kujoth et al. (2005) [59] conducted a study where they induced a mitochondrial mutation in mice, and reported early signs of aging, including presbyacusis. They cloned the mouse POLG locus (*PolgA*). Polg gene (mitochondrial DNA polymerase gamma) was identified as a cause of several human disorders such as Alpert syndrome and sensory disorders such as hearing loss [60]. With the use of gene targeting in embryonic stem cells, they induced an AC→ CT two-base substitution (corresponds to position 1054 and 1055 of the *PolgA* cDNA). The result of this mutation was a critical residue substitution in the conserved exonuclease domain of POLG, disturbing its proofreading ability. The mutation produced $PolgA^{D257A/+}$ mice, which were intercrossed to generate homozygous $PolgA^{D257A/D257A}$ mice. At 2 months of age, there was no difference in auditory-evoked Brainstem Responses (ABR) analysis between the wild-type and D257A mice, however, at 9 months of age, a premature aging phenotype began, in the form of hair graying, hair loss and kyphosis with a marked elevation of ABR thresholds (4, 8, and 16 kHz), indicating severe hearing loss. Histological studies revealed age-related loss of spiral ganglion neurons. Sarcopenia (loss of muscular tissue), which is another sign of aging, was also present in D257A mice. The mechanisms that results in premature cochlear degeneration are, so far, not clear although there was a clear evidence of apoptosis, but not accumulation of oxidative damage [59, 61, 62].

Preliminary results of Ibrahim et al. (2017) (see chapter 3 below) showed that although auditory input does not seem to have a significant influence on postural stability in normal hearing individuals, it does significantly improve postural stability in some hearing impaired individuals who use hearing aids. Whether there are mitochondrial deletions/mutations that affect both cochlear and vestibular tissues as opposed to deletions/mutations that affect solely the cochlear tissues, or that the same mitochondrial deletions/mutations affect both the cochlear and vestibular tissues either simultaneously or consequently, it is of great importance to investigate this topic. This would give more insight when counselling hearing impaired patients, drawing their attention to the importance of amplification, not only for hearing, but also for postural stability and safety, and maybe providing vestibular rehabilitation alongside with auditory rehabilitation.

1.2. Thesis rationale and objectives

Based on the studies listed above, there is a great potential that auditory input may affect postural stability. However, this is not yet well demonstrated. Sound localization ability particularly seems an important aspect, since sound localization cues are processed at an earlier stage, before the auditory input reaches the IC, where its potential contribution to postural stability might take place.

In this thesis, I hypothesize that the presence of a stable sound source will result in improved postural stability, and that the ability to correctly locate sound sources will be associated with the ability to maintain postural stability and balance. In addition, I want to evaluate the mitochondrial mutations associated with balance disorder that occur with prebyastasis. Early detection of those mutations in patients with presbyacusis might lead to preventive measurements to improve the quality of life in old age.

As a result, the objectives of this thesis are: 1) to conduct a literature review on the possible interaction(s) between hearing and balance. 2) to evaluate effects of cochlear-implant surgery on postural stability and vestibular function, 3) to determine whether providing an auditory input results in improved postural stability in both normal subjects and hearing aid users, characterizing the effect of this auditory input on postural stability, and 4) to conduct a literature

review to investigate mitochondrial DNA mutations/deletions and their possible association with hearing and balance disorders.

1.3. Linking statement to first manuscript

This chapter described the potential interactions between hearing and balance. Many interactions have been reported between the two in cochlear implant candidates and users. Also, the presence of an objective and/or subjective decline in vestibular function among cochlear implant candidates and the experience of post-operative balance disorders among cochlear implant users has been reported in the literature. However, there has been wide variation in the reported degree of decline. Such uncertainty was the motivation to conduct a systematic review and meta-analysis to study of the effect of cochlear-implant surgery on balance and vestibular function as assessed using several objective & subjective measures.

Chapter two: Effect of Cochlear Implant Surgery on Vestibular Function: Meta-analysis study (Manuscript 1)

Iman Ibrahim: M.Sc. Student, Department of Otolaryngology-Head and Neck Surgery, McGill University.
Email: iman.ibrahim@mail.mcgill.ca

Sabrina Daniela da Silva: Assistant Professor, Department of Otolaryngology-Head and Neck Surgery, Jewish General Hospital, McGill University.
Email: sabrina.wurzba@mcgill.ca

Bernard Segal: Professor, Department of Otolaryngology-Head and Neck Surgery, Jewish General Hospital, McGill University.
Email: bernard.segal@mcgill.ca

Anthony Zeitouni: Associate Professor**,** Department of Otolaryngology-Head and Neck Surgery, Royal Victoria Hospital, McGill University.
Email: anthony.zeitouni@mcgill.ca

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2.1. Abstract

Importance: Vestibular disorders have been reported following cochlear implant (CI) surgery, but the literature shows a wide discrepancy in the reported clinical impact. The aim of this meta-analysis is to quantify the effect of CI before and after surgery on the outcomes of vestibular tests, postural stability, and subjective perception of dizziness.

Objective: To evaluate the effects of CI surgery on vestibular function in adult patients (≥18 years) with sensorineural hearing loss who underwent unilateral or bilateral implantation.

Data sources: MEDLINE, PubMed, Web of Science and Cochrane Library from January 1, 1995, through July 12, 2016.

Study selection: Published studies of adult patients who received unilateral or bilateral CIs and whose vestibular function or postural stability was assessed before and after surgery.

Data extraction: From each study, test results before and after surgery were compared, for the following five tests: clinical head impulse test (HIT); bi-thermal caloric irrigation of the horizontal semicircular canal; vestibular evoked myogenic potential (VEMP); dizziness handicap inventory (DHI); and computerized dynamic posturography (CDP).

Results: Twenty-seven studies met all inclusion criteria. Most studies performed either bi-thermal caloric irrigation and/or VEMP, with fewer studies investigating changes in HIT, posturography or DHI. CI surgery significantly affected the results of caloric and VEMP testing. However, HIT results, posturography, and DHI, scores were not significantly affected after CI surgery.

Conclusions and relevance: CI surgery has a significant negative effect on the results of caloric as well as VEMP tests. No significant effect of CI surgery was detected in HIT, posturography, or DHI scores. Overall, the clinical effect of CI surgery on the vestibular function was found to be insignificant. Nonetheless, the potential effects of surgery on the vestibular system should be discussed with CI candidates before surgery.

KEYWORDS: Cochlear Implant, Vestibular function, Postural stability, Vestibular disorders.

2.2. Introduction

Hearing loss is the most common sensory deficit of all. More than 5% of the world's population suffer from disabling hearing loss, affecting about one-third of people above 65 years of age [63]. In cases where hearing aids are no longer useful or sufficient, cochlear implant (CI) surgery is the standard procedure for the treatment of hearing loss. CI attempts to replace the function of hair cells that are no longer able to stimulate primary auditory neurons in response to sound. While the effects of CI surgery on residual cochlear function is well studied, less attention has been given to its effects on vestibular function. Such effects occur because CI surgery frequently affects the vestibular apparatus, which is in close anatomical proximity to the auditory system.

Different mechanisms that could lead to vestibular dysfunction during or after CI surgery have been postulated: 1) direct trauma caused by electrode insertion, 2) acute serous labyrinthitis due to cochleostomy, 3) foreign body reaction with labyrinthitis, 4) endolymphatic hydrops, and 5) electrical stimulation from the implant itself [10].

The occurrence of vestibular dysfunction following CI surgery has a very wide range as assessed by bi-thermal caloric testing and vestibular evoked myogenic potential (VEMP) testing [10, 38, 39, 40, 42]. However, not all CI recipients suffer from postoperative dizziness [10,38, 39, 42], and CI recipients reported different forms of dizziness after surgery. Postoperative dizziness had different characteristics, onset, and duration [40].

Given the increasing use of bilateral implantation, it would be important to be able to quantify the effects of CI surgery on the vestibular system. This information would be of great benefit both to the CI team and patients. The aim of the current study was to evaluate the effects of CI surgery on vestibular function and postural stability in adult patients having sensorineural hearing loss (SNHL) who underwent unilateral or bilateral implantation. The purpose of the current meta-analysis study was to demonstrate a quantifiable effect of CI surgery on several tests for balance and vestibular function.

2.3. Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement was used as our methodology for this systematic review [64].

Study eligibility criteria

The criteria used in the selection were: (1) studies including adult patients (≥ 18 years old), (2) studies reporting both pre- and postoperative test results, and (3) studies that reported numbers of normal and abnormal patients for the following tests: clinical head impulse test (HIT), caloric, and vestibular evoked myogenic potential (VEMP) testing were included. Studies that reported raw or average data and standard deviations for posturography (Sensory Organization Test (SOT) conditions 5 and 6) or for dizziness handicap inventory (DHI) pre- and postoperatively were also included. Studies involving young patients (< 18 years) were excluded.

All studies had CI surgery performed by the same surgical unit, so it was assumed that the techniques between patients were standardized.

Data sources

A thorough search of MEDLINE, PubMed, EMBASE, Web of Science and Cochrane Review was conducted, using the keywords "cochlear implant and vestibular" or "cochlear implant and caloric" or "cochlear implant and VEMP" or "cochlear implant and balance" or "cochlear implant and posturography" or "cochlear implant and dizziness" or "cochlear implant and Dizziness Handicap Inventory". This meta-analysis included the date range from January 1st, 1995 to July 12th, 2016.

Data extraction

A total of 2006 potential journal articles was identified using the keywords mentioned above. Only articles in English and French were included. Individual studies' abstracts were screened to select the studies that met the criteria for this meta-analysis. Full texts of selected articles were retrieved and then rescreened for possible inclusion in the current meta-analysis by two different observers independently.

Data presentation

Different tests exist to evaluate different aspects of the state of the vestibular apparatus. The HIT is one test that assesses vestibulo-ocular function. Other tests objectively evaluate parameters associated with different parts of the vestibular apparatus; however, they do not measure the function of the vestibular system. Such tests include the caloric and VEMP tests.

Posturography is a set of tests that assess the integrative vestibular performance associated with maintenance of posture, where the vestibular function integrates with other sensory inputs (such as vision & proprioception, in order to maintain posture). When applying the SOT test, posturography assesses the state of compensation, because all the movements are sway-referenced, with no induced movements. The DHI is a subjective test for assessment of the perceived function of the vestibular balance condition.

Data synthesis

Four separate meta-analyses were conducted - one for each test. For HIT, caloric, and VEMP testing, the outcome measure was obtained from the ratio of subjects with normal test results before and after surgery; the effect size was measured using the log relative risk (RR) because outcomes are reported in a dichotomous manner (i.e. either normal or hypo/areflexia). For Posturography and DHI, the outcome measure was the mean difference in scores; the effect size was measured using the mean difference (MD) in scores before and after surgery. The random effects model was used, because of the expected variability in the tests' conditions and results interpretation in the different test centers, and also because all the heterogeneity analyses were significant. Due to the low number of studies available, a meta-analysis was not performed for the posturography data. To calculate the mean difference in scores, the means and standard deviations for scores were extracted, as well as the number of subjects before and after surgery. All data analyses were performed using R-version-3.1.2. Statistical significance was defined as $P < 0.05$.

2.4. Results

Of the 2006 studies, 1956 articles were excluded at the abstract level because they were either duplicates or because the eligibility criteria did not apply (Fig. 2.1). Next, the full-text of 50 publications were recovered, and then 23 of these publications were excluded because it was not possible to extract useful data from them. Those reports either did not report numbers of subjects having preoperative normal vestibular function and/or numbers of subjects having postoperative normal vestibular functions, or they applied different forms of tests not evaluated in this study. The remaining 27 reports were included in the meta-analysis (Fig. 2.1) and the results were described separately (Table 2.1., Fig. 2.2-2.5).

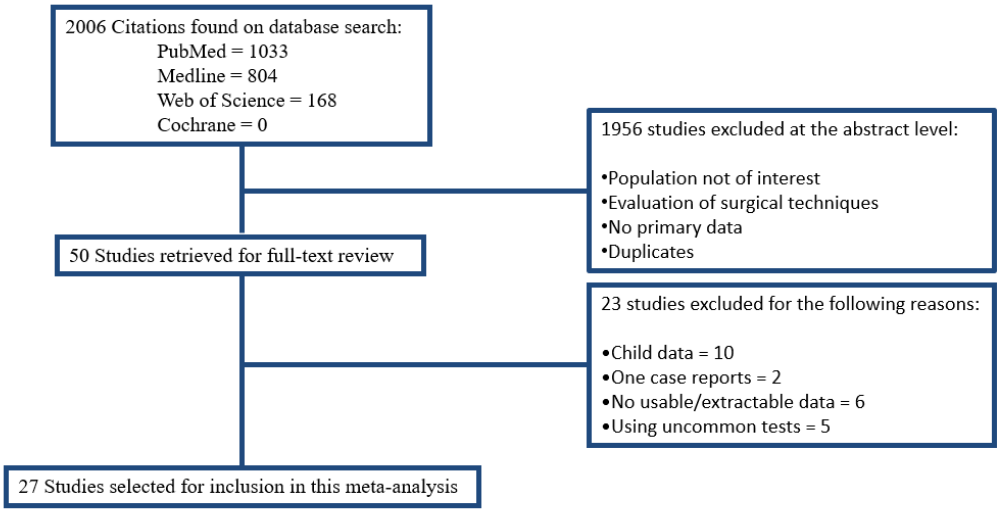

Fig. 2.1. Flow diagram of search and study selection process

Table 2.1. Summary of results of all studies included in the meta-analyses.

Source (publication)	Study design	Follow-up (days)	Number of patients	Mean age (range)	HIT + RE	Caloric + RE	VEMP + RE	DHI+ RE	CDP + RE
Abramides 2015 [41], Sao Paolo, Brazil	Prospective study	120	24	42 (12–65)		Yes $P = 0.414$			
Basta 2008 [69] Berlin, Germany	Prospective study	42	18	(10–75)	Yes ND (NS)	Yes ND (NS)	Yes $P < 0.05$	Yes ND (NS)	
Bateucas 2015 [65] Salamanca, Spain	Prospective descriptive	2	30	54 ± 10	Yes	Yes			
Bonucci 2008 [72] Sao Paolo, Brazil	NI*	NI*	38	30.65 ± 32 4–62		Yes ND			
Brey 1995 [71] Mayo clinic,Rochester, Minnesota	NI*	45 to 1770	52	3-87		Yes P = 0.01			Yes ND
Buchman 2004	Prospectivestudy	30	67	2-87				Yes	Yes

[42] University of North Carolina, USA								ND	ND
Coordes 2012 [70] Berlin, Germany	Prospective study	NI*	17	60 (20–73)			Yes ND		
Ernst 2006 [86] Berlin, Germany	Prospective study	365	18	18-62			Yes ND (NS)		
Ito 1998 [87] Otsu, Japan	NI*	30	55	>18		Yes ND			
Jutila 2012 [88] Helsinki, Finland	Prospective study	60	44	55 (30–76)	Yes P > 0.05				
Katsiari 2013 [10] Piraeus, Greece	Prospective study	30	20	47.6 ± 20.2 10–77		Yes *P* = 0.01	Yes *P* = 0.002		
Kiyomizu 2000 [89] Miyazaki, Japan	NI*	NI*	23	36-75		Yes ND			

Kluenter 2009 [40] Fena, Germany	Prospective study	42 31–368)	52	47(11–74)		Yes ND			
Kluenter 2010 [81] Fena, Germany	Prospective study	44 (31–363)	24	51 (20–75)		Yes ND			
Krause 2009a [78] Munich, Germany	Prospective study	28 - 42	59	54 (15–83)		Yes $P < 0.001$			
Krause 2009b [80] Munich, Germany	Prospectivestudy	28	47	54 (16–83)		Yes $P < 0.01$			
Krause 2010 [79] Munich, Germany	Prospectivestudy	60	32	55 (15–83)		Yes $P < 0.001$	Yes $P < 0.047$		
Louza 2015 [90] Munich, Germany	Retrospective observational study	28 - 42	41	>14 56 ± 19		Yes ND	Yes ND		
Melvin 2009 [39] Johns Hopkins, Maryland, USA	Prospective cohort	28 - 42	16	46 (23–69)	Yes ND	Yes ND	Yes ND		

Migliaccio 2005 [67] Johns Hopkins, Maryland, USA	Prospective study	28 - 42	16	46 (27–64)	Yes $P > 0.05$				
Nordfalk 2014 [77] Oslo, Norway	Prospective pilot	28 - 42	12	32-61			Yes ND		
Nordfalk 2015 [75] Oslo, Norway	Prospective	42-56	39	57.5 ± 17.2 (18–83)		Yes ND	Yes ND		
Robard 2015 [68] Caen, France	Prospective study	150	34	49 ± 25 (1–86)			Yes $P = 0.0015$		
Rossi 1998 [91] Turin, Italy	Case series	180	32	12-74		Yes ND			
Todt 2008 [92] Berlin, Germany	Retrospective cohort	42 - 56	62	17-84		Yes ND	Yes ND		
Vankatova 2014 [66] Geneve, Switzerland	Retrospective study	NI*	50	15-72	Yes ND	Yes ND			

Wagner 2010 [73] Berlin, Germany	Retrospective cohort	42 - 56	20	41.5 (11–58)		Yes ND	Yes ND		

*HIT** head impulse test, *VEMP** vestibular evoked myogenic potential, *DHI** dizziness handicap inventory, *CDP** computerized dynamic posturography, *RE** reported effect, *NI** not identified. *ND** not detected, *NS** non-significant, *S** significant. *RE** reported effect

HIT results

The number of subjects with normal and abnormal testing results before and after CI surgery who were included in the meta-analysis of the HIT test is shown in Table 2.2. (Appendix). The statistical analysis revealed a non-significant effect of CI surgery on the HIT test results (RR = 0.0951, 95% CI = -0.0220, 0.2122, *P* = 0.11). There was substantial variability in the results observed in these studies (I^2 = 57.98%, QDF = 5) = 11.2612, *P* = 0.046). The forest plot indicating the relative strength of each study included in the meta-analysis is illustrated by Fig. 2. Two studies (Batuecas et al., 2015 [65] and Vankatova et al. 2014 [66]) had a relatively larger number of abnormal postoperative HIT results. However, patients in Batuecas et al. [64] were re-tested after a relatively short postoperative period (two days). For Vankatova et al. [66], communication with the authors revealed that they had false positive results. Consequently, it was decided to exclude this study from the meta-analysis.

Five out of the six studies that performed HIT, conducted a quantitative HIT, whether a video HIT [65, 66], a search coil HIT [40, 80], or a motorized HIT (mHIT) [83]. Only Basta et al., 2008 [69] used a bedside HIT.

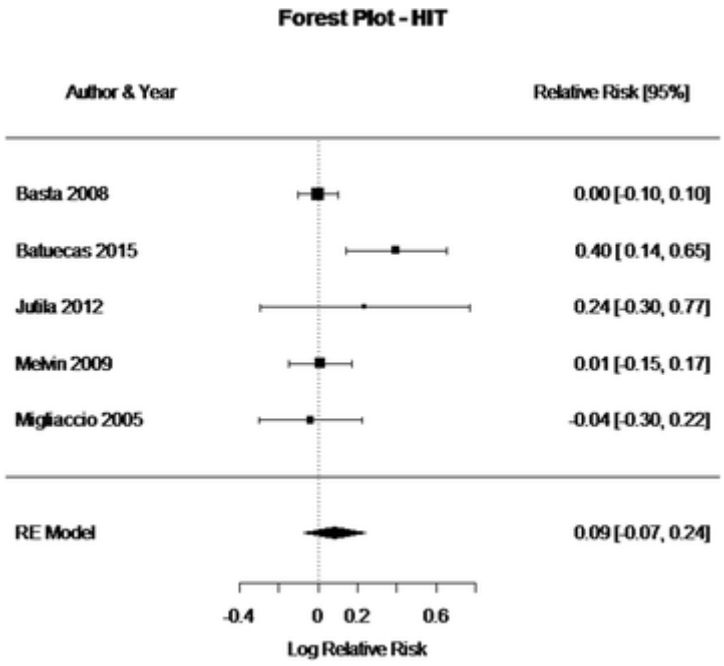

Fig. 2.2. Forest plot (showing relative effect sizes) for the HIT test.

Caloric test results

The number of subjects with normal and abnormal testing results before and after CI surgery included in the meta-analysis of the caloric test is shown in Table 2.3. (Appendix). The statistical analysis revealed a significant effect of CI surgery on the caloric test results (RR = 0.2826, 95% CI = 0.1032, 0.4621, *P* = 0.0039). There was a considerable heterogeneity observed in the studies (I^2 = 74.90%, Q (DF = 18) = 50.8956, *P*<0.0001). The forest plot indicating the relative strength of each study included in the meta-analysis is illustrated by Fig. 3. Despite the variability among the reports, the results revealed a tendency for loss of peripheral vestibular function following CI surgery in the majority of the 19 studies involved in this analysis. Several factors could account for the variability among the studies, such as the age range, the test settings and timing of the postoperative retest.

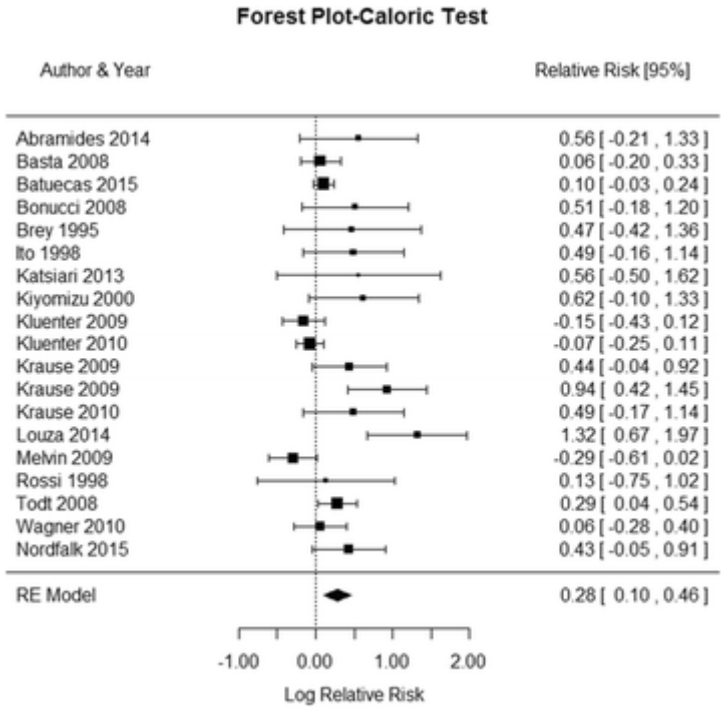

Fig. 2.3. Forest plot (showing relative effect sizes) for the caloric test.

VEMP test results

The studies included in the meta-analysis of VEMP test are shown in Table 2.4. (Appendix). All included studies used cVEMP. The statistical analysis revealed a significant detrimental effect of CI surgery on VEMP test results (RR = 0.5099, 95% CI = 0.2941, 0.7256, $P < 0.0001$). There was a substantial heterogeneity in the studies ($I^{2} = 51.68\%$, Q (DF = 11) = 20.7693, $P= 0.0293$). The forest plot indicating the relative strength of each study included in the meta-analysis is illustrated by Fig. 4. Two studies (Coordes et al. 2011 [70], and Melvin et al. 2009 [61]) had a relatively higher number of patients who retained normal VEMP test results postoperatively. This could be due to the use of bone-conduction VEMP, which is more sensitive compared to air-conduction VEMP [70].

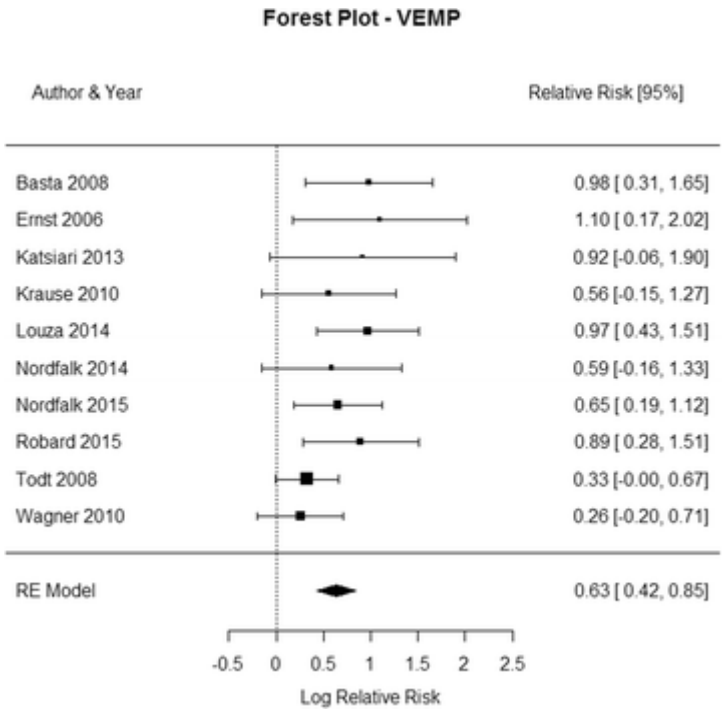

Fig. 2.4. Forest plot (showing relative effect sizes) for the VEMP test.

Posturography results

The results from the studies that investigated posturography, particularly the conditions 5 and 6 are shown in Table 2.5. (Appendix). Meta-analysis could not be conducted because only two studies were retrieved [42,12]. Brey et al. 1995 [71]. found a non-significant difference between pre- and post- implantation, where the difference in conditions 5 and 6 scores was very subtle: These results did not differ much from the results reported by Buchman et al. 2004 [42]. Overall, postural stability performance did not seem to be affected by the CI surgery.

DHI results

Results from the studies that were included in the meta-analysis of the DHI test are shown in Table 2.6. (Appendix). The statistical analysis revealed a non-significant effect of CI surgery on the DHI scores (MD= -14.9718, 95% CI = -44.1804, 14.23, P = 0.3151). There was a considerable heterogeneity in the studies (I^2 = 98.65%, Q (df = 3) = 280.0102, P.0001). The forest plot showing the relative strength of each study included in the meta-analysis is illustrated by Fig. 5. Basta et al., 2008 [68] reported an unusually high postoperative mean score. However, these authors analyzed only five patients with a significant increase in their DHI scores after the surgery. All of them were significantly older (68.8 ± 6.5 years), as compared to the other studies (mean 46.7 ± 18.2 years). Results from DHI scores agree with posturography results, where in most studies, even those reporting increased DHI scores did not result in a change that required further investigation and/or intervention.

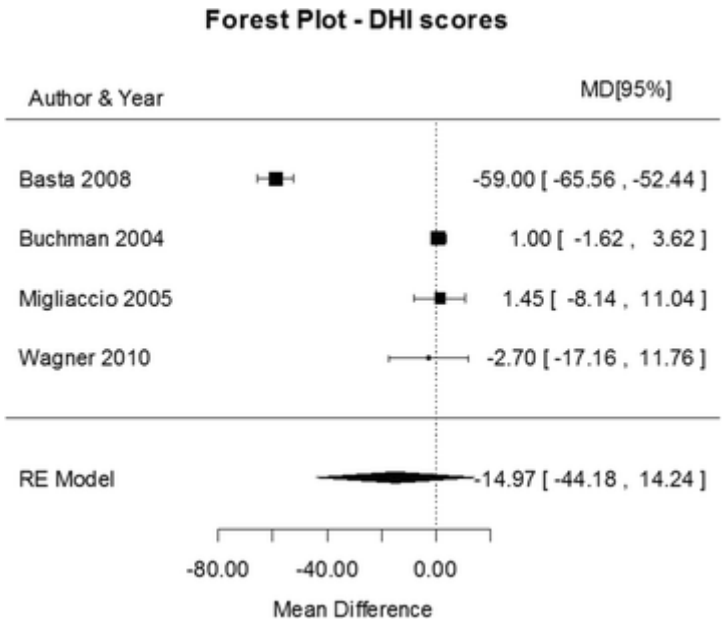

Fig. 2.5. Forest plot (showing relative effect sizes) for the DHI test.

2.5. Discussion

Vestibular disorders have been reported following CI surgery. This systematic review and meta-analysis showed great variability in the tests' results. This variability might be due to the different testing measures employed. Both HIT and caloric tests are strongly affected by the lateral semicircular canal function. VEMP testing is strongly influenced by the saccular function. Posturography testing is closely related to the compensatory mechanisms of postural performance. DHI assessments characterize a patient's subjective impression about their balance perception. Thus it appears that CI may affect some aspects of vestibular function. [40]. The variability may also be partly explained by the differences in the criteria and/or test techniques such as the cut-off to determine the normal *versus* abnormal test results [10]. However, not all studies reported their criteria.

Two studies [65, 66] had a relatively larger number of abnormal postoperative HIT results. Maybe this can be explained by the short postoperative re-test period (two days) [65]. Unfortunally, was not possible to pool and analyze studies based on follow-up periods because

several papers were not specific, either they did not specify the period [72], or provided a very wide range for it [71].

For VEMP results, two studies [39,70] showed better postoperative results. This could be due to the use of bone-conduction VEMP, which is more sensitive compared to air-conduction VEMP [70], and hence were not included in the meta-analysis. For DHI results, Basta et al., [69] reported an unusually high postoperative mean score. However, these authors analyzed only five patients with a significant increase in their DHI scores after the surgery. All of them were significantly older (68.8 ± 6.5 years), as compared to the other studies (mean 46.7 ± 18.2 years). Results from DHI scores agree with posturography results, where in most studies, even those reporting increased DHI scores did not result in a change that required further investigation and/or intervention.

Another factor that contributes to variability of the results is the fact that CI users are not a homogenous population. They come from different age groups involving newborns to older adults suffering from severe-to-profound SNHL. Thus, age and etiology of SNHL can affect the vestibular function either before, after, or both before and after CI surgery. For example, meningitis often results in disturbed vestibular function due to ossification of the labyrinth (Cushing et al., 2009 [73]). From the pooled results in the current meta-analysis, it was found that before surgery, 39.5% had abnormal caloric test results, 31.7% had abnormal VEMP test results, and 11.5% had abnormal HIT results [see Table 2.1. and appendix]. Two studies [79, 86] showed a preoperative average DHI scores higher than 10 indicating a previous vestibular problem. Few studies reported the number of patients with preoperative caloric or VEMP hyporeflexia who had a deterioration (areflexia) postoperatively [10, 66, 68]. For example, Bonucci et al. 2008 [71] found that 10% of the patients who had preoperative hyporeflexia in the caloric test had postoperative areflexia, however, it was not clear whether it was the implanted ear or the contralateral ear. Abramides et al. 2015 [41] and Katsiari et al. 2013 [10] reported that a deterioration in the non-implanted ear might occur either because the insertion of the electrode in the scala tympani in one ear alters the vestibular input to the brain, and hence modifies the contralateral ear response, or because the reproducibility of the response in these individuals over time is not perfect.

Surgical technique can also affect the outcome. Factors such as electrode insertion site (whether through a cochleostomy, anteroinferior to the round window, or directly through the round window), the electrode length (short or long electrode), the electrode insertion speed, and the electrode insertion depth [81]. The current literature does not provide details about the surgical procedure and only mention the technique used (cochleostomy *versus* round window approach). The majority of the articles reported the cochleostomy (anteroinferior to the round window) as the standard approach[1]. Unfortunally, it was not mentioned whether soft surgical techniques were used to minimize trauma to the labyrinth [76].

The data in the current meta-analysis showed no significant increase in DHI in the majority of patients (84.4%), suggesting that CI did not affect balance. Seventy-two percent of the patients retained a normal caloric function after surgery, 60% retained normal HIT results, and 56% retained normal VEMP test results, thus it can be concluded that the impact of CI surgery on the vestibular apparatus was not clinically significant. It is worth noting that some conditions such as the use of ototoxic drugs or Meniere's disease might be present in CI users, and could limit the interpretation of abnormal balance tests in case testing was done only postoperatively. However, the studies did not report detailed patients' medical history to be conclusive.

It is important to note that some studies were performed by the same group (Nordfalk et al. [75, 77], Krause et al. [78, 79, 80], and Kluenter et al. [40, 81]). The authors were contacted to verify whether these studies have an overlap. Nordfalk et al. have different sets of patient populations, so they do not overlap. Kluenter et al. had 12 patients who participated in both studies. No response was received from Krause et al.

We found that CI surgery can significantly affect the results of both the caloric test and VEMP test. This finding is in accord with the systematic review of Kuang et al. [82], where they found that 37% of patients had reduced reflex, and 34% had caloric asymmetry after CI surgery. Other authors [83, 84] reported that one-third of CI recipients complain of dizziness after surgery. A recent review aimed at determining the best test to evaluate vestibular function before and after CI surgery was published by Abouzayd et al., 2016 [85]. They found that the caloric test was least sensitive, VEMP results were most often impaired, and HIT results were generally

[1] Todt et al., 2008 [92] claimed that the use of round window approach for electrode insertion would decrease the probability of loss of vestibular function postoperatively, compared to the standard cochleostomy approach.

conserved. Our study provides a quantified evidence that CI surgery can significantly affect some vestibular test results (although it might not be clinically significant, as evident from the pre- and postoperative DHI scores). It also provides estimates of vestibular dysfunction in CI candidates. The current study confirms that it is important to pursue a case-by-case approach with CI surgery candidates, based on each patient's history and symptoms.

To summarize, several factors can contribute to the variability of the results within and between the vestibular function tests, both before and after CI surgery, that are difficult to control for. Those factors include age and etiology of hearing loss, the surgical technique used, and the incidence of trauma to the inner ear. Because congenital, genetic, and post-meningitis hearing loss is more common in children, a separate analysis of pediatric vestibular function before and after CI surgery, and comparing the results to adults, would be a useful area of future research.

2.6. Conclusion

According to the results of the current meta-analysis, CI surgery can significantly affect the results of caloric as well as VEMP tests. No significant effect was detected in HIT results, posturography, or DHI scores. Drawing a definitive conclusion is rather difficult for a number of reasons, such as heterogeneity in study design, variability among patient populations, pre-existing condition, and measurement and reporting differences. While studies showed that some postoperative scores were worse after CI, the proportion of patients affected appears low. Age and etiology of hearing loss appear to affect the vestibular function after CI surgery. Nonetheless, the possible effects of CI surgery on the vestibular system should be communicated to CI recipients before surgery.

ABBREVIATIONS

CI: Cochlear Implant

DHI: Dizziness Handicap Inventory

HIT: Head Impulse Test

MD: Mean Difference

RR: Relative Risk

SOT: Sensory Organization Test

VEMP: Vestibular Evoked Myogenic Potential

2.7. Declaration

Ethics approval and consent to participate: Not applicable. .

Consent for publication: Not applicable.

Availability of data and material: Data sharing not applicable to this article as no datasets were generated or analysed during the current study

Competing Interests: The authors declare that there is no conflict of interest regarding the publication of this paper.

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2.9. Authors Contribution

Iman Ibrahim: data collection, data analysis, manuscript drafting.
Sabrina Daniela da Silva: data analysis, manuscript editing and revision.
Bernard Segal: data analysis, manuscript editing and revision.
Anthony Zeitouni: Concept & design, data analysis, manuscript editing and revision.

2.10. Linking statement to second manuscript

The results of this review and meta-analysis showed that CI surgery can significantly affect the results of caloric as well as VEMP tests, while no significant effect was detected in HIT results, posturography, or DHI scores. It appeared that age and etiology of hearing loss were important factors that can affect the overall balance abilities. According to the current study results, a considerable percent of cochlear implant candidates have balance disorders and/or vestibular hypo- or areflexia. Whether hearing loss can have a negative effect on balance even at earlier stages of hearing loss, where the patient can use hearing aids, and whether correcting the hearing loss with the proper hearing aid can improve balance performance, are the questions that I tried to answer in the second manuscript. The second manuscript is a clinical study that evaluates the role of auditory inputs in maintaining postural stability both for normal hearing individuals and for hearing aid users.

2.11. Appendix

Table 2.2. Number of subjects with normal and abnormal testing results before and after surgery in studies included in the meta-analysis for the HIT test. Normal pre = number of individuals with normal test results before surgery. Abnormal Pre = number of individuals with abnormal test results before surgery. Normal post = number of individuals with normal test results after surgery. Abnormal post = number of individuals with abnormal test results after surgery. Number pre= number of individuals tested before surgery. Number post = number of individuals tested after surgery.

Study	Year	Normal pre	Abnormal pre	Normal post	Abnormal post	Number pre	Number post
Basta[69]	2008	18	0	18	0	18	18
Batuecas[65]	2015	30	0	20	10	30	30
Jutila[88]	2012	19	25	15	29	44	44
Melvin[39]	2009	14	0	10	0	14	10
Migliaccio[67]	2005	14	2	10	1	16	11
Vankatova[66]	2014	50	0	43	7	50	50

Table 2.3. Number of subjects with normal and abnormal testing results before and after surgery in studies included in the meta-analysis for the caloric test. Normal pre = number of individuals with normal test results before surgery. Abnormal Pre = number of individuals with abnormal test results before surgery. Normal post = number of individuals with normal test results after surgery. Abnormal post = number of individuals with abnormal test results after surgery. Number pre= number of individuals tested before surgery. Number post = number of individuals tested after surgery.

Study	Year	Normal Pre	Abnormal pre	Normal post	Abnormal post	Number pre	Number post
Abramides[41]	2014	14	34	8	40	24	24
Basta[69]	2008	16	2	15	3	18	18
Batuecas[65]	2015	30	0	27	3	30	30
Bonucci[72]	2008	15	23	9	29	38	38
Brey[71]	1995	8	9	5	12	17	17
Ito[87]	1998	18	37	11	44	55	55
Katsiari[10]	2013	7	13	4	16	20	20
Kiyomizu[89]	2000	13	10	7	16	23	23
Kluenter[62]	2009	18	6	21	3	24	24
Kluenter[81]	2010	41	11	44	8	52	52
Krausea[78]	2009	25	20	15	27	45	42
Krauseb[79]	2009	35	21	13	40	56	53
Krause[80]	2010	13	9	8	14	32	32
Louza[90]	2014	30	11	8	33	41	41
Melvin[39]	2009	14	6	15	1	20	16
Nordfalk[75]	2015	20	10	13	17	30	30
Rossi[91]	1998	8	24	7	25	32	32
Todt[92]	2008	48	14	36	26	62	62
Wagner[74]	2010	17	5	16	6	22	22

Table 2.4. Number of subjects with normal and abnormal testing results before and after surgery in studies included in the meta-analysis for the VEMP test. Normal pre = number of individuals with normal test results before surgery. Abnormal Pre = number of individuals with abnormal test results before surgery. Normal post = number of individuals with normal test results after surgery. Abnormal post = number of individuals with abnormal test results after surgery. Number pre= number of individuals tested before surgery. Number post = number of individuals tested after surgery.

Study	Years	Normal. pre	Abnormal. pre	Normal. post	Abnormal. post	Number. Pre	Number. post
Basta[69]	2008	16	2	6	12	18	18
Coordes[70]	2012	17	0	14	3	17	17
Ernst[86]	2006	12	6	4	14	18	18
Katsiari[10]	2013	10	10	4	16	20	20
Krause[80]	2010	14	16	8	22	30	30
Louza[90]	2014	29	12	11	30	41	41
Melvin[61]	2009	12	7	11	5	19	16
Nordfalk[77]	2014	9	3	5	7	12	12
Nordfalk[75]	2015	25	8	13	20	33	33
Robard[67]	2015	22	12	9	25	34	34
Todt[92]	2008	39	23	28	34	62	62
Wagner[74]	2010	22	18	17	23	20	20

Table 2.5. Test results (Sensory Organization test scores) before and after surgery in studies included in the meta-analysis for the posturography test. Mean1 = mean scores before surgery. SD1 = scores standard deviations before surgery. Number1 = number of patients tested before surgery. Mean2 = mean scores after surgery. SD2 = scores standard deviations after surgery. Number2 = number of patients tested after surgery.

Study	Year	Mean1	SD1	Number1	Mean2	SD2	Number2
Brey[71]	1995	46.99	25.68	22	45	31.04	22
Brey[71]	1995	43.5	22.1	22	42.17	28.76	22
Buchman[42]	2004	39	26	82	40	27	67
Buchman[42]	2004	33	26	82	31	26	67

Table 2.6. Test results (DHI scores) before and after surgery in studies included in the meta-analysis for the DHI test. Mean1 = mean scores before surgery. SD1 = scores standard deviations before surgery. Number1 = number of patients tested before surgery. Mean2 = mean scores after surgery. SD2 = scores standard deviations after surgery. Number2 = number of patients tested after surgery.

Study	Year	Mean1	SD1	Number1	Mean2	SD2	Number2
Basta[69]	2008	5	1.41	18	64	14.14	18
Buchman[42]	2004	5	8	78	4	8	66
Migliaccio[67]	2005	10.54	11.76	11	9.09	11.18	11
Wagner[74]	2010	14.9	24.4	20	17.6	22.2	20

Chapter three: Postural stability: Assessment of auditory input in normal hearing individuals and hearing aid users (Manuscript 2)

Iman Ibrahim: M.Sc. Student, Department of Otolaryngology-Head and Neck Surgery, McGill University.

Email: iman.ibrahim@mail.mcgill.ca

Sabrina Daniela da Silva: Assistant Professor, Department of Otolaryngology-Head and Neck Surgery, Jewish General Hospital, McGill University.

Email: sabrina.wurzba@mcgill.ca

Bernard Segal: Professor, Department of Otolaryngology-Head and Neck Surgery, Jewish General Hospital, McGill University.

Email: bernard.segal@mcgill.ca

Anthony Zeitouni: Associate Professor**,** Department of Otolaryngology-Head and Neck Surgery, Royal Victoria Hospital, McGill University.

Email: anthony.zeitouni@mcgill.ca

Corresponding Author: Dr. Iman Ibrahim

iman.ibrahim@mail.mcgill.ca

Manuscript in Preparation for **Laryngoscope**.

Preliminary versions of this study have been presented at

Conférence Annuelle De L'Association Québécoise des Orthophonistes et Audiologistes (AQOA), Québec

April 2017.

3.1. Abstract

Background: Dizziness is the most common complaint of patients over 65 years consulting a physician. Presbyacusis affects 65% of Canadians ageing 70 to 79. The inner ear is responsible for both hearing and postural stability. However, the interactions between auditory information and the maintenance of postural balance have not been widely studied. The ability to localize sounds requires calibration of the auditory input at both ears, and could correlate with better postural stability.

Objectives: To evaluate the effect of auditory input on postural stability for normal hearing subjects and hearing-aid users.

Methods: The effect of auditory input on postural stability, as well as the sound localization abilities in normal hearing adults, was assessed with and without the use of earplugs in normal subjects, and in adult hearing users with and without hearing aids. Balance Tests (Romberg on foam and tandem stance) were performed in the presence of a point-source of noise in both groups. Sound localization was performed using both high- and low- pass Narrow-band noise sounds.

Results: Normal individuals' balance performance was not affected by the absence of auditory input. However, hearing aid users had significant better balance with hearing aids on for the Romberg test ($P = 0.012$), and for the Tandem test ($P = 0.011$). Also, hearing aid users had a significantly improved sound localization with their hearing aids on ($P = 0.008$).

Conclusions: Auditory input does not seem to have an effect on postural stability in normal hearing individuals. However, hearing impaired individuals and hearing aid users had a significant improvement in their postural stability in the presence of an auditory input.

Keywords: Presbyastasis, auditory input, sound localization, postural stability.

3.2. Introduction

Age-related hearing loss is a gradual and progressive deterioration in hearing. It is a multifactorial process, resulting from a combination of various factors such as genetic predisposition, vascular and cognitive impairment, loss of auditory neurons (e.g., spiral ganglion neurons), and deterioration of cochlear hair cells [93]. In Canada, presbyacusis occurs in 38.3% of those aged 60-69 and in 65% of those aged 70-79 [94]. Dizziness is the most common complaint in patients over 65 consulting a physician. However, the interactions between auditory information and the maintenance of postural balance have not been widely studied [34, 95]. It is not widely recognized that poor hearing may increase fall risk.

Postural regulation is the result of dynamic processing of multiple sensory inputs by the central nervous system. There are well-known contributions of musculoskeletal, visual, proprioceptive, and vestibular information to the maintenance of postural balance and stability. However, the contribution of auditory inputs to postural stability has been under-investigated [32].

In normal health individuals, even with eyes closed, the ability to localize the direction of a sound source is accurate to within a few degrees in the horizontal plane. The term “spatial hearing” refers to the ability to localize sound sources, taking advantage of the temporal and spectral differences between the acoustic signals reaching both ears. Spatial hearing enables listeners to detect sounds in challenging acoustic conditions [96, 97]. The ability to localize sound increases the awareness of the surrounding environment, and hence is an important source of information that improves balance control and postural stability.

Presbyacusis is the most common type of sensorineural hearing loss. It is an age-related process, where most hearing loss occur in the high-frequency region. In order to determine if hearing aid usage might improve postural balance, it would be of great importance to know whether boosting such higher frequencies with hearing aids might substantially improve postural stability more than simply transmitting low frequencies, which are usually heard normally in most cases of presbyacusis. The goal of the current study is to investigate the role of auditory input in postural stability, particularly high-frequency auditory input, and to test the association between sound localization abilities and postural stability.

3.3. Materials & Methods

3.3.1. Participants

This study was approved by the Research Ethics Committees of the Royal Victoria Hospital and the Jewish General Hospital (McGill University - Canada). Patients were advised of the procedures and then they provided written informed consent. Ethical guidelines were followed and clinicopathological data were handled in a coded fashion. Twenty-one normal hearing individuals were recruited, however, four of them were found to have high frequency hearing loss when hearing screening was performed prior to testing. Nine hearing aid users were recruited from the audiology clinics of the Royal Victoria Hospital and the Jewish General Hospital. The sample size was determined using Horatio software [98]. The software suggested a minimum sample size of 23 individuals, alpha level of 0.05, a medium effect size, measurement of independent variables within subjects, and a power of 0.80.

3.3.2. Sound localization test

Horizontal sound localization, particularly front-back localization was tested. Two stimuli were used: low-pass (<2 kHz) and high-pass (> 2 kHz) Narrow Band Noise. Stimuli were presented at 30 dB SL from two speakers, at +45° and +135°. Each sound was played from each speaker six times. With two conditions per person (with & without hearing aid or earplug), the total trials per person was: Stimuli: 2(aid/plug-use) x 2(sound frequencies) x 6(repeats) x 2(speakers) = 48 total. This setting for sound localization is similar to the home-based training setting conducted by Kuk et al. (2014) [99].

3.3.3. Tests for postural stability

Participants were asked to complete the well-known Dizziness Handicap Inventory (DHI) [100]. Romberg and tandem postural tests were used to assess postural stability. For the Romberg on foam test, participants were asked to take off their shoes and stand on a foam pad (Muscle Up Balance Pad, from Muscle Up Canada), with feet together, with eyes closed, and with arms crossed above their shoulders. The goal was to maintain balance for 30 seconds. For

the Tandem test, participants were asked to place their dominant foot in front of the other in a heel to toe fashion. The goal was to maintain this posture for 30 seconds. Each test was conducted three times for each condition: (a) without hearing aids, and with hearing aids for hearing aid users, and (b) with and without earplugs for normal hearing individuals. All tests were done in the presence of 1/3 octave noise (center frequency ~3 kHz), emitted from a speaker placed directly in front of the subject (at 0° azimuth). Trials were randomized to avoid possible training effects and/or fatigue.

3.3.4. Selection Criteria

The inclusion criteria included normal hearing individuals, as well as hearing aid users, age 18+ years. Hearing aid users who had unilateral or bilateral moderate-to-severe sensorineural hearing loss required a history of at least 6 months of hearing aid use.

The exclusion criteria included patients who had balance disorders that would likely increase the risk of falling during the objective balance tests (Romberg and Tandem tests). Subjects using medications that could cause hearing loss or could affect balance; patients with walking aids; and patients with a history of stroke were excluded from the study.

3.4. Results

A total of 21 normal hearing participants were enrolled (13 females and 8 males; mean age 37.1 ±15.9). Participants without a recent hearing test were screened using an online hearing test [101]. After screening, four participants were excluded from the normal-hearing group because of high frequency hearing loss at 4 & 8 kHz (three males & one female; age range (57 to 70 years). However, they were tested, and their results are discussed in comparison with the 17 normal hearing individuals (mean age 29.5 ± 11.4).

The DHI contains 25 questions. A total score (ranging between zero to 100 points) is obtained by summing ordinal scale responses, with higher scores indicating a more severe handicap. Results for DHI questionnaire averaged 1.0 ± 2.6. with one participant scoring 10, two scoring 4, one

scoring 2, and the remaining 13 normal hearing individuals as well as the four hearing impaired individuals scoring 0.

Figure 3.1. compares the balance tests results of the three groups tested: normal hearing individuals, individuals with mild hearing loss at high frequencies (presbyacusis), and hearing aid users who had moderate-through-severe sensorineural hearing loss. A significant worsening in balance tests' scores of hearing aid users compared to normal hearing individuals was observed (P = 0.0003). Further analysis of the results for each test separately also revealed a significant decrease in hearing aid users' scores for the Tandem test (P = 0.032), and the Romberg on foam test (P = 0.00064).

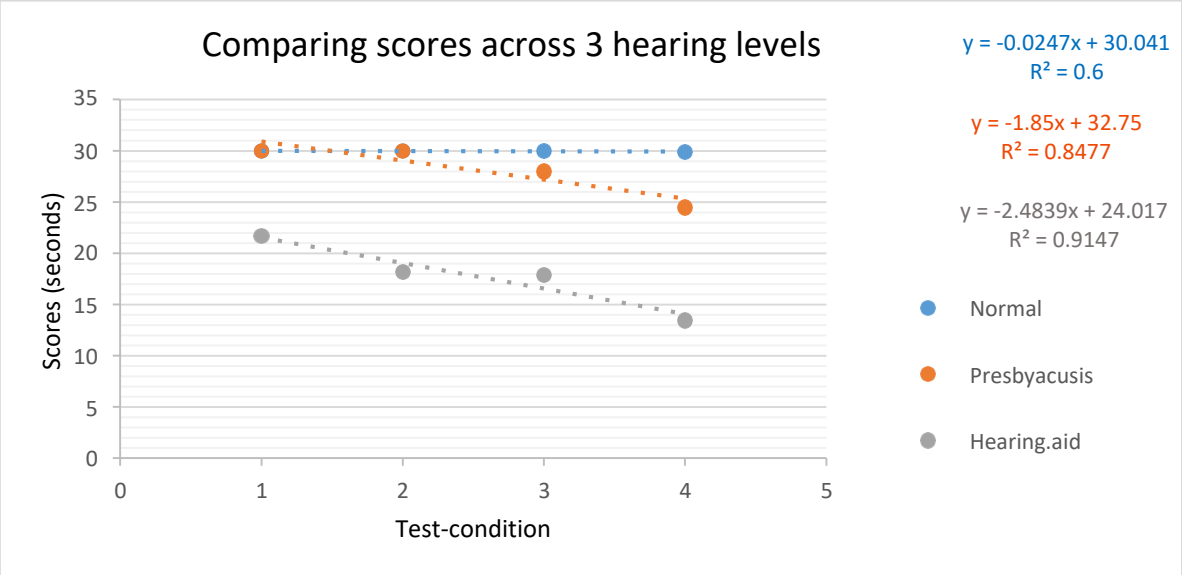

Figure 3.1. Balance test results in (a) normal hearing (top), (b) Presbyacusis (middle), and c) Hearing aid users (bottom). The x axis shows the test condition: 1) Tandem (without ear plugs for groups a & b, and with hearing aids for group c; 2) Tandem (with ear plug for groups a & b, and without hearing aids for group c; 3) Romberg on foam (without ear plug for groups a & b, and with hearing aids for group c; 4) Romberg on foam (with ear plug for groups a & b, and without hearing aids for group c. The y-axis shows the interval (in seconds) before losing balance. Tests were stopped after 30 s.

Results for balance tests (Romberg on foam and Tandem stance tests) for the 17 normal hearing individuals and 4 hearing impaired individuals are shown in Figure 3.2. For Tandem stance, all 17 normal hearing participants were able to stand for 30 seconds with or without the earplugs. Also, for the Romberg on foam test, they were all able to stand for 30 seconds without earplugs. When earplugs were used, all could stand for 30s, except for 2 subjects, yielding an average performance of 29.9 ± 0.2 seconds. The four hearing impaired participants had similar results for Tandem stance, all of them were able to maintain 30 seconds with and without the use of earplugs, however, 2 of them were not able to maintain 30 seconds in Romberg on foam test, with or without earplug. Their average was 28 ± 3.4 without earplugs, and 24.5 ± 5.8 seconds with earplugs.

Nine hearing aid users were tested (mean age 58.5 ± 21.2 years). Their mean score for the DHI questionnaire was 10 ± 11.2. Figure 3.3 shows the results of the balance tests for these patients. The results were as follows: Tandem without hearing aid: 18 ± 8.8 seconds. With hearing aid use, performance improved to 21.5 ± 8.2 seconds. Romberg on foam test without hearing aid: 13.3 ± 9.2 seconds. With hearing aid use, performance improved to 17.9 ± 8.4 seconds. Eight out of the nine patients had better scores in the aided condition compared to the unaided condition in the Romberg test; the ninth scored the maximum of 30 seconds under both conditions. Similarly, eight patients had better scores in the aided compared to the unaided condition in Tandem test, while the ninth scored better under the unaided condition. A two-tailed Wilcoxon sign-ranked test indicated a significant difference between balance performance in the aided versus the unaided condition in both the Romberg on foam test ($P = 0.012$), and the Tandem test ($P = 0.011$). The mean improvement with the hearing aid use was 3.36 seconds for the Tandem, and 4.4 seconds for the Romberg on foam tests.

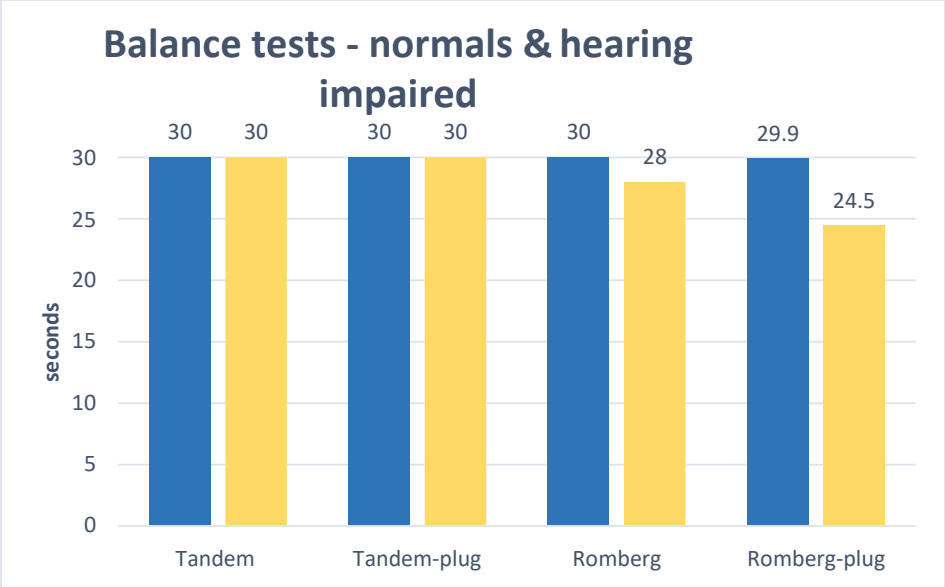

Fig. 3.2. Results of Romberg and Tandem tests for balance for normal hearing and hearing impaired individuals. (normal hearing in blue and hearing impaired in yellow).

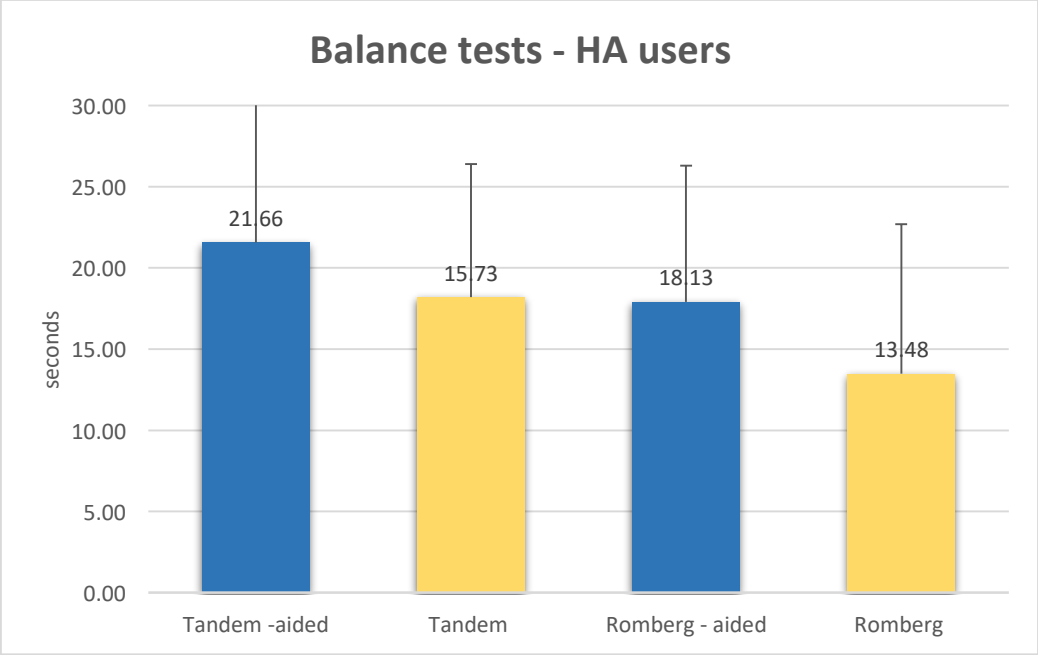

Fig. 3.3. Results of Romberg and Tandem tests for balance for hearing aid users. (aided in blue and unaided in yellow).

Results for sound localization tests for the 17 normal hearing individuals and four hearing impaired listeners are shown in Figure 3.4. Normal hearing participants had an average correct score of 80% (±16) for the low-pass filtered sound, and 90% (±13) for the high-pass filtered sound without earplugs. When earplugs were used, their performance decreased, particularly for the high-pass sound. Scores with earplugs were 69% (±13) for low-pass, and 60% (±20) for high-pass sounds. Hearing impaired individuals had the lowest scores among the three groups. Their scores were 51% (±13) for the low-pass, and 55% (±8) for the high-pass sounds without earplugs. With the use of earplugs, their performance was 58% (±28) for the low-pass, and 52% (±25) for the high-pass sound. Comparing the normal hearing and the hearing impaired listeners' scores for sound localization test revealed significantly lower scores for hearing impaired listeners ($P = 0.046$).

Results for the sound localization test for five out of the nine hearing aid users who completed the localization task are shown in Figure 3.5. Their average scores were: 50.1% (±24) for low-pass, and 64.5% (±22) for high-pass sounds, without the use of hearing aids. When they used their hearing aids, their scores increased to 71.6% (±29) for low-pass, and 76.8% (±26) for high-pass sounds. A two-tailed Wilcoxon sign-ranked test showed a statistically significant difference between the aided and unaided localization performance ($P = 0.008$).

No association between balance test scores and sound localization scores was observed. There was no clear trend between the ability to localize sounds and balance tests' performance.

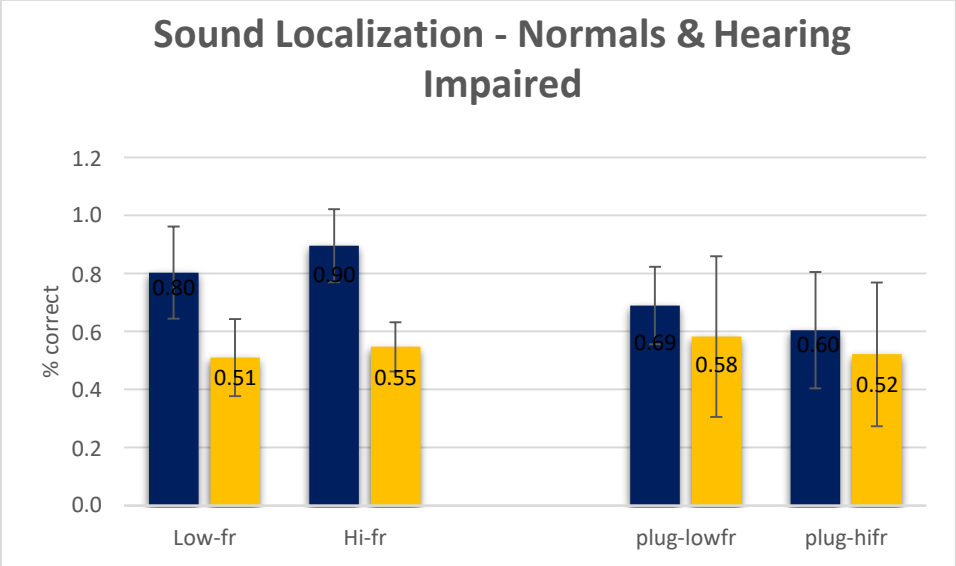

Fig. 3.4. Sound localization test results for normal hearing and hearing impaired individuals. Low-fr: Low-frequency; Hi-Fr: High-frequency. (normal hearing in blue and hearing impaired in yellow).

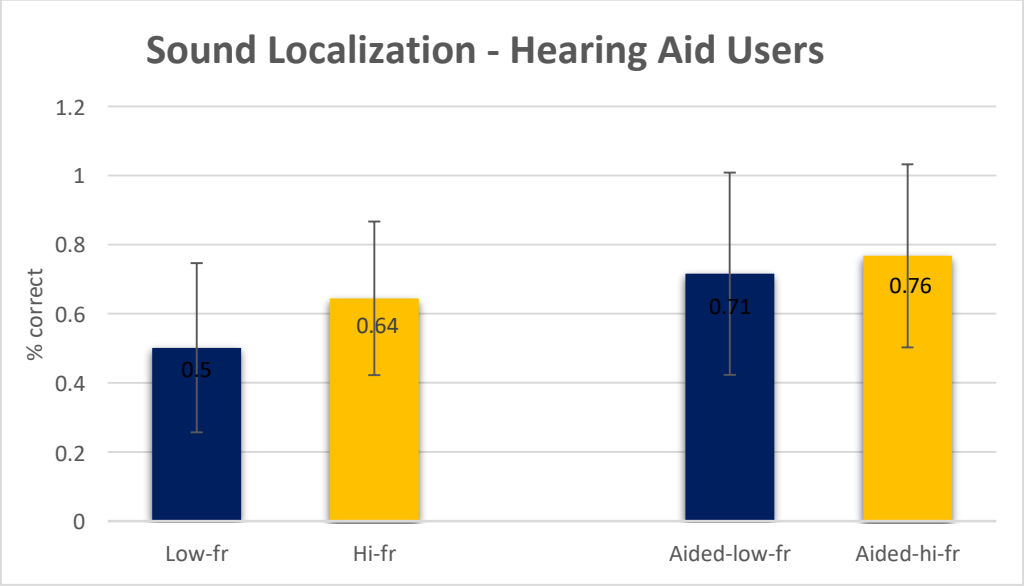

Fig. 3.5. Sound localization test results for hearing aids user. Low-fr: Low-frequency; Hi-Fr: High-frequency (low frequency in blue and high frequency in yellow).

3.5. Discussion

Falls have been identified as the one of the most frequent cause of mortality in the USA after highway accidents [102]. Twenty percent of non-fatal cases involving days away from work was caused by fall related incidents [103]. The annual direct cost from occupational injuries due to falls in United States was estimated to exceed $6 billion [104]. Because about 19% of the US workforces are aged 55 or older [105], fall-related costs in the working elderly probably exceed $1 billion; costs of the more-frequent elderly fall at home would probably be even larger. The morbidity from a fall is proportionally higher on older individuals.

A Study by Gago et al. (2015) [106] found that auditory input improves the central control of postural stability, although it has a smaller influence than vision. Rumalla et al. (2015) [32] assessed postural stability performance in hearing aid users, under various conditions showing that performance was significantly better in aided users compared to unaided users. However, these authors used a Broadband noise sound source). Sakellari & Soames (1996) [37] showed that different sound intensities and/or frequencies could have different effects on postural sway.

The current study investigated the role of auditory input in postural stability, particularly high-frequency auditory input, and the correlation between sound localization abilities and postural stability. Our results show that hearing level had a significant effect on postural stability, as assessed using the Tandem-stance and Romberg-on-foam results. These results showed that for hearing impaired individuals and hearing aid users, auditory input helped with the maintenance of postural stability. This result was different for normal hearing individuals, for whom auditory input had a very minimal role in postural stability. Statistical analysis revealed a significant improvement in both Romberg on foam and Tandem stance tests under the aided condition. It was clear that the hearing aids were helping the hearing-aid users maintain better balance, in fact, six of them stated during the interview that their hearing aids provide them with better awareness of their environment.

A recent study by Rumalla *et al.*, (2015) [32] investigated the benefit of hearing aid use for hearing impaired listeners in postural stability also found a significant improvement in balance in older adults with aided compared to the unaided condition. They hypothesized that auditory input provided by the hearing aids provided a spatial orientation landmark, and in that case, the brain

relied on the sound localization ability, where the input from both ears might have been compared at the medial and lateral superior olivary complexes, in order to create a 3D map of sound sources around the body, and hence maintain balance by the relationship between the body and this landmark constant.

A direct relation between hearing loss and the risk of fall was also reported. For example, Lin et al., (2012) [107] found 1.4 times increased fall risk for each 10 dB of hearing loss. Similarly, Rumalla *et al*. [32] reported that risk of falling in the unaided condition is 1.67 times the risk of falling in the aided condition.

Our current study also investigated the association between sound localization ability, and balance performance in both normal hearing and hearing aid users. We used a sound localization setting similar to the home-based training setting conducted by Kuk et al. (2014) [100]. The results of normal hearing individuals were consistent with the literature in that front-back scores were slightly better for high frequencies. However, when the external ear was blocked with earplugs, the scores for high frequencies were worse compared to those for the low frequencies, because the pinna cues were disrupted [108]. The hearing impaired listeners, despite having a mild high-frequency hearing loss, had a poor performance, compared with both normal hearing and hearing aid users. Previous studies have shown that the correlation between the degree of hearing loss and sound localization abilities is rather weak [108, 109].

Hearing aid users had a better performance during high frequency stimuli compared to low-frequency sound, with a significant improvement in their performance under the aided condition. However, an association between sound localization abilities and balance performance was not established in our study. For normal hearing listeners, the ceiling effect (i.e., limited duration) of the balance tests might have prevented observation of further improvement. Also, for the hearing users, the wide variability of the balance and localization test results might have made it difficult to observe a clear trend. Further studies are necessary to clarify the relationship between hearing levels and postural stability, and to investigate any possible confounding factors, such as age and/or other morbidities.

3.6. Conclusion

Although auditory input did not have an effect on postural stability of normal hearing individuals, the hearing aid users that were evaluated showed a significant improvement in their postural stability in the presence of auditory inputs, as well as an improvement in their sound localization abilities. We found no association between the ability to localize sounds and postural stability in the current data.

3.7. Declarations

The investigators do not have any conflicts of interest to declare. This study was funded by OSAP, a CIHR grant (Canada Graduate Scholarships Master's (CGS M) Award 2015-2016 to Iman Ibrahim, and by the Department of Otolaryngology Head & Neck Surgery.

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3.9. Author Contribution

AZ: concept & design, data analysis, manuscript revision. BS: concept & design, data analysis, manuscript revision, SDS: data analysis, manuscript revision, II: data collection, data analysis, manuscript drafting.

3.10. Linking statement to third manuscript

The above study showed that while auditory inputs may not have an effect on postural stability in normal hearing individuals, auditory inputs did improve balance in hearing impaired individuals and in hearing aid users. The study also showed that older adults (whether they had normal hearing, mild presbyacusis, or sensorineural hearing loss and were hearing aid users) tended to exhibit improved postural stability in the presence of auditory inputs. However, younger adults, even if they used hearing aids, tended to show minimal improvement, or no change, in postural stability in the presence of auditory inputs. This tendency was the motivation to conduct a systematic review to investigate the molecular basis for presbyacusis and presbyastasis, and to investigate the possibility that known DNA mutations - particularly mitochondrial DNA mutations - that are believed to result in a gradual decline in hearing ability with age might also be responsible for a decline in postural stability. The review is presented in the next chapter.

Chapter four: Mitochondrial mutations associated with hearing and balance disorders (manuscript 3)

by

Iman Ibrahim[1], Mev Dominguez Valentin[2], Bernard Segal[3], Anthony Zeitouni[1], Sabrina Daniela da Silva[3*]

[1]Department of Otolaryngology-Head & Neck Surgery, Royal Victoria Hospital, McGill University

[2]Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway

[3]Department of Otolaryngology-Head & Neck Surgery, Jewish General Hospital, McGill University

***Corresponding Author**

Sabrina Daniela da Silva

Department of Otolaryngology-Head and Neck Surgery - McGill University

Lady Davis Institute for Medical Research and Segal Cancer Centre

Sir Mortimer B. Davis-Jewish General Hospital,

3755 Côte Ste-Catherine Road, Montreal, Quebec H3T 1E2, Canada

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Preliminary versions of this study have been presented at

The Eighth Annual Lady Davis Institute (LDI) Scientific Retreat, Montréal in May 2017.

4.1. Abstract

Balance disorders can lead to falls. The inner ear is responsible for both hearing and balance. Hearing loss that commonly occurs with aging (aka presbyacusis) can result from noise exposure, smoking, ototoxic drugs and genetic factors such as mitochondrial mutations. In this study, we evaluate the mitochondrial mutations associated with balance disorder that occur with prebyastasis. Early detection of those mutations in patients with presbyacusis can generate preventive measurements to improve the quality of life on old age.

Keywords

Mitochondrial mutation, hearing loss, balance disorders, presbyastasis, presbyacusis.

4.2. Background

Balance disorders may result in falls and fall-related injuries, which affect 30% of people above 60 years old [110, 111]. In this sense, presbyacusis (aka age-related hearing loss) is the third most prevalent chronic health problem among older adults in North America. Similar to presbyacusis, impairment of vestibular function associated with aging (aka presbyastasis) have an impact for elderly. Both affect about 33.3% patients around 65 years, and up to 80% of those > 85 years [112]. The signs of presbyacusis includes difficulty hearing in noisy venues, asking people to repeat what they have said, difficulties hearing sounds with high frequencies, mainly consonants (such as d, t, th, s, f, sh), which usually carry the meaning of words, and hence, speech intelligibility decreases leading to social isolation. The ability to localize sounds is crucial for survival since it directs the attention to potential sources of danger and alerts [96]. However, no significant association between the degree of hearing loss and the decline to localize sounds have been reported [109].

Hearing impairment can be due to central or peripheral causes and the most common site of injury is the middle ear and cochlea. Histological changes included primary degeneration of the cochlear neurons [113]. Emerging large-scale studies on the genetic architecture have indicated that hearing loss is usually polygenic in nature: their phenotypic variance is influenced by many genetic variants simultaneously, each which of only contributes a very small fraction of the

variance [114]. The difficulty in identifying genetic factors suggests that presbyacusis is a multifactorial disease involving a complex interaction of genetic and environmental factors [115].

Mitochondria are considered one of the main factors in the progression of presbycusis and presbyastasis [116]. These organelles are responsible for vital cellular functions, including energy production, apoptosis, cell signaling, and calcium storage [117]. The malfunction in energy supply by mitochondria is often associated with mitochondrial DNA (mtDNA) deletions. Tissues or organs with the highest ATP requirements, including the inner ear, are more likely to show a higher proportion of deleted mtDNA. Furthermore, DNA repair mechanisms are less well developed in the mitochondria than in the nucleus [43, 118, 119]. The clinician must have a thorough knowledge of the potential complications of mitochondrial disorders to prevent unnecessary morbidity. Advances in the understanding of the intracellular mechanisms underlying presbyacusis could lead to the development of diagnostic markers and therapies to decrease or reverse the changes in the auditory system.

This study presents an overview of the molecular nature of the age related hearing loss and its association with mitochondrial mutations. We show potential preventive measurements that may improve the quality of life in older adults.

4.3. Mitochondria; function in normal tissues

Mitochondria are 0.5–1 mm intracellular organelles in size and are bound by two membranes. They are the intracellular organelles mainly responsible for the cellular adenosine triphosphate (ATP) production by oxidative phosphorylation (OXPHOS). Apart from the nucleus, only mitochondria have their own DNA (mtDNA), and they play very important dual role by providing more than 80% of the energy required by the cell to function and grow, as well as regulating programmed cell death (apoptosis) and oxidative stress control. The total mtDNA represents about 0.5% of the total DNA in a nucleated somatic cell. mtDNA consists of 16,569 base pairs of DNA and encode for 37 genes (two rRNAs, 22 tRNAs and 13 polypeptides) (figure 4.1.) [117, 120].

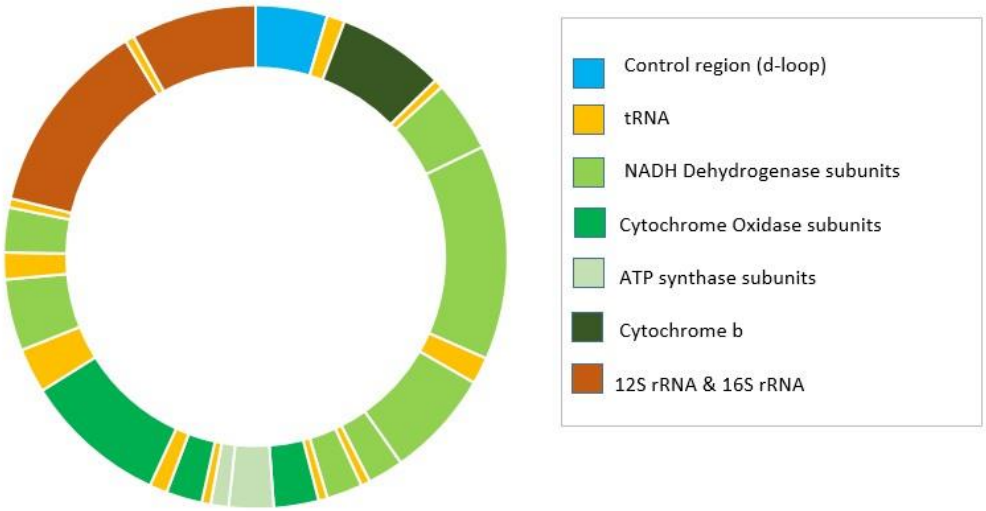


Fig.4.1. Structure of mtDNA molecule.

Mitochondrial genes are located close to each other (37 genes on 16.5Kb). The mtDNA has no introns, only a non-coding region used to produce polycistronic RNA transcripts, which are subsequently cleaved to produce tRNAs, rRNAs, and mRNAs.

One of the main function of mitochondrias is the generation of ATP, by catalyzing the phosphorylation of cellular adenosine diphosphate (ADP) and supply energy. Along with approximately 60 nuclear encoded proteins, the 37 mitochondrial genes form five enzyme complexes of the respiratory complex required for OXPHOS: complex I reduced nicotinamide adenine dinucleotide dehydrogenase, complex II, complex III cytochrome c oxidoreductase, complex IV cytochrome c oxidase, and complex V ATP synthetase [43] (**Figure 4.2**). All the diseases caused by mutations in the mitochondrial genome are characterized by OXPHOS defects.

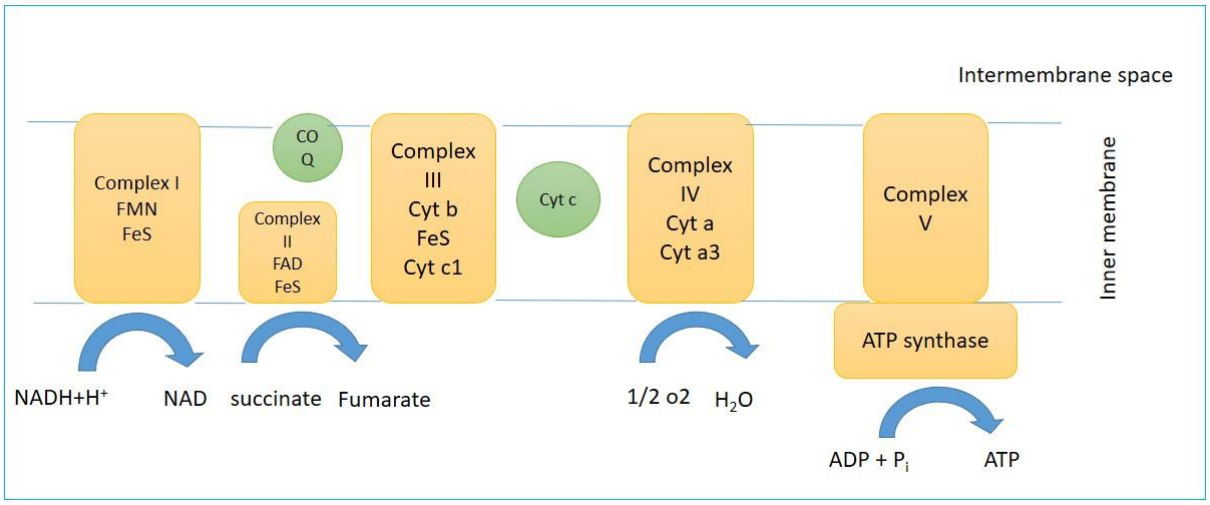


Fig. 4.2. Five enzyme complex of the respiratory chain complex, that catalyze the OXPHOS process in mitochondria.

4.4. Mitochondria and their relation with diseases

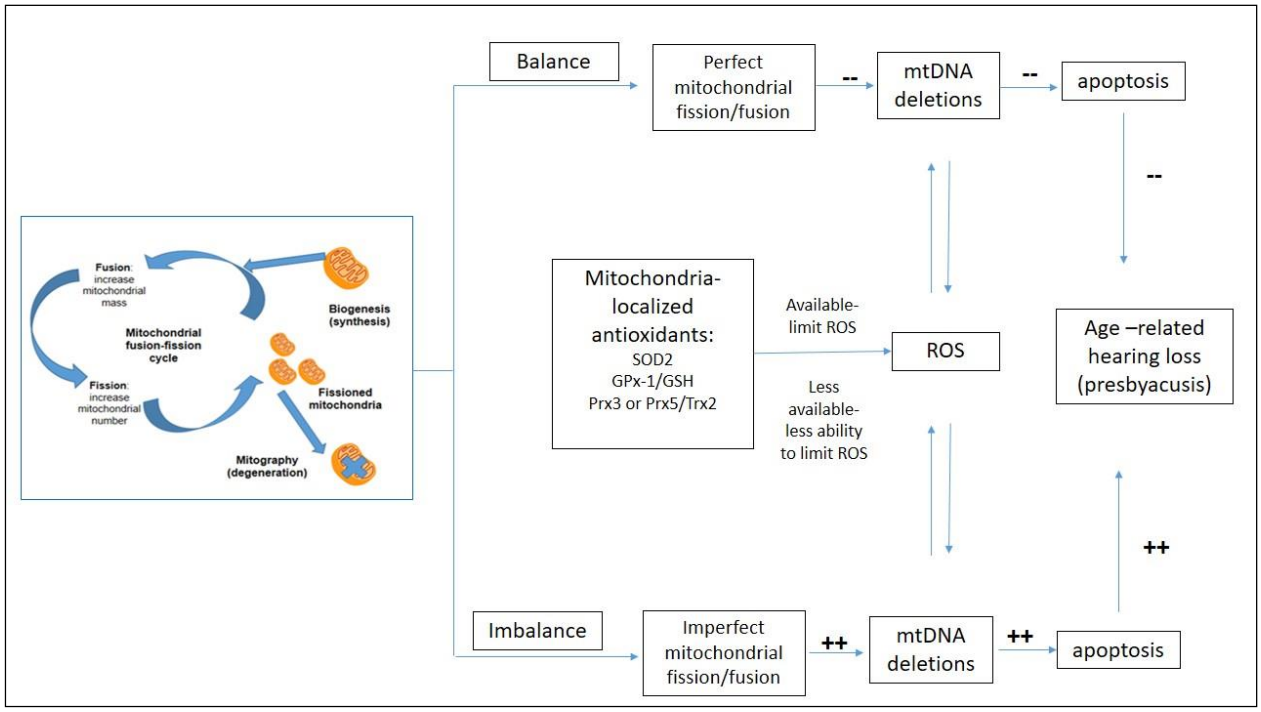
The prevalence of all mitochondrial disorders is 11.5: 100,000 (~1:8500) [121] and may be manifested at any age. Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain (**Figure 4.2.**). They can be caused by mitochondrial mutation or large rearrangements in one of the 60 nuclear genes or in one of the 37 mitochondrial genes encoding proteins. Nuclear gene defects may be inherited in an autosomal recessive or autosomal dominant manner. mtDNA deletions generally occur *de novo* and thus cause disease in one family member only, with an approximate recurrence risk of 1 in 24. mtDNA single-nucleotide variants and duplications may be transmitted down the maternal line [122]. Most of the mitochondrial mutations are collected in the human mitochondrial genome database MITOMAP (http://www.gen.emory.edu/mitomap.html).

Mitochondrial disorders can affect a single organ e.g., the eye in Leber hereditary optic neuropathy and the ear in non-syndromic hearing loss with or without aminoglycoside sensitivity. However, mtDNA mutation can lead to multisystem disorders and often present with prominent neurologic and myopathic features such as Kearbs-Sayre syndrome (KSS); neurogenic

weakness; ataxia and retinitis pigmentosa (NARP); myoclonic epilepsy; lactic acidosis; and stroke-like episodes (MELAS); or mitochondrial ragged red fibers (MERRF), Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis [122,123,124,125]. The clinical diseases ensue when the proportion of mutant mtDNA exceeds a certain threshold at which deleterious consequences of the mutation are no longer compensated for the wild-type mtDNA. The management of mitochondrial disease is largely supportive and may include early diagnosis and treatment. Individuals with complex I and/or complex II deficiency may benefit from oral administration of riboflavin; those with ubiquinone (coenzyme Q10) deficiency may benefit from oral coenzyme Q10 therapy; and those with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) may benefit from early hematopoietic stem cell transplantation [122].

4.5. Mitochondria mutation and hearing loss and balance

Audiological data obtained from patients carrying mtDNA mutations show that the hearing loss is always sensorineural, usually progressive and for the most part symmetrical [126]. Because of the difficult in obtaining cochlear material, only a limited number of biological studies have been published [117]. Comparative post-mortem temporal bone analysis showed a significant increased level of mtDNA mutations in cochlear tissues from individuals who had presbyacusis compared to normal hearing individuals (deletion level of 32 ± 14 % in the presbyacusis group, compared to 12 ± 2 % in the control group) [127]. The progressive breakdown of mitochondrial function in presbyacusis, might be because of the interplay of environmental factors with the accumulation of mutations in the nuclear or mtDNA susceptibility genes. Previous studies demonstrated the role of OXPHOS and excessive reactive oxygen species (ROS) in presbyacusis development [127, 128]. Major ROS production pathways include OXPHOS dysfunction, increased pro-ROS enzyme activity, and decreased anti-ROS activity is playing important roles in hearing loss (**Figure 4.3.**).



Several rare mutations in mtDNA encoding rRNA (*MTRNR1*) or tRNA (*MTTS1*) have been found to be responsible for hearing loss. Specific mutations in the *MTRNR1* gene (i.e., 961delT/insC, T1095C, C1494T, A1555G, A827G, T1005C or A1116G) and *COI/MTTS1* gene (G7444A) are associated to ototoxic hearing loss (**Table 1**). Mutations in *MTRNR1* were linked to maternally inherited hearing loss, which in most cases is induced or aggravated by ototoxic aminoglycosides such as gentamicin, kanamycin, and streptomycin [129] (**Table 4.1**). *MTRNR1* mutation (961delT/insC, T1095C, C1494T, A1555G) has been described in Chinese sporadic patients and large number of Italian families with aminoglycoside ototoxicity [130, 131, 132]. Two percent of the patients with sensorineural hearing loss had high frequency of this mutation [133] raising the possibility of a relatively high prevalence of this mutation among hearing-impaired populations. Other genetic variants (T1005C, A1116G, T1243C and T129C) might play a role in aminoglycoside ototoxicity but with unknown penetrance [133] (**Table 4.1**). In the same way, A827G mutation has been associated with the pathogenesis of hearing impairment. However, incomplete penetrance of hearing loss indicates that A827G mutation alone is not

sufficient and requires the involvement of modifier factors for the phenotypic expression [134] (**Table 4.1 near here**).

Mutations in the *MTTS1* gene have been detected in association with sensorineural hearing loss: these include the A7445G mutation, the insertion of a deoxycytidine nucleotide at position 7472 (7472insC), and three T to C transitions at positions 7510, 7511, and 7512 (T7510C, T7511C, and T7512C), respectively (**Table 4.1**) [135]. The mutation leaves the structure of the tRNA intact but affects the rate of processing of the tRNA precursor, resulting in a reduction in the tRNA level. Management issues may include early diagnosis and treatment such as cochlear implantation for sensorineural hearing loss. A variety of vitamins and co-factors have been used in individuals with mitochondrial disorders, although a Cochrane systematic review has shown that evidence supporting their use is lacking [122]

Preliminary results (Ibrahim et al. 2017, unpublished data) showed that although in normal hearing individuals auditory input does not seem to have a significant influence on postural stability, it does improve postural stability in some hearing-impaired individuals who use hearing aids. Whether there are mtDNA mutations that affect cochlear and/or vestibular tissues either simultaneously or consequently, it was not subject of investigation yet. This would give more insightful information when counselling hearing impaired patients, drawing their attention to the importance of amplification, not only for hearing, but also for postural stability and safety, and maybe providing vestibular rehabilitation alongside with auditory rehabilitation.

4.6. Therapeutic Strategies for mtDNA Disease

Mitochondrial diseases related to defective mtDNA have previously been treated empirically with variable combinations of co-factors and vitamins, a “mito-cocktail” frequently including antioxidants such as quinones (CoQ and idebenone), lipoic acid, vitamins E and C, and molecules boosting bioenergetics such as creatine and carnitine [136].The efficacy of these treatments has been unclear due to the intrinsic difficulties in running properly designed controlled trials with rare diseases, with mitochondrial disorders posing additional problems due to their clinical heterogeneity and loosely defined natural history [137].

At genetic level, the lack of tools to manipulate the multi-copy mtDNA genome, delimited by a double membrane, has been a major obstacle. However, major breakthroughs have been achieved recently, opening a new era for the therapy of mitochondrial disorders. Translational evidence from both patients [138] and animal models [139] is strategy for the compensatory activation of mitochondrial biogenesis. Multiple approaches have converged on activating the transcriptional co-activator PGC1α, the master regulator of mitochondrial biogenesis [140, 141]. A deeper understanding of the basic biology of mitochondria holds promise for developing effective therapies, which for most mitochondrial diseases currently remain at the level of palliative and symptomatic approaches.

Table 4.1. Mitochondrial mutations leading to syndromic and non-syndromic hearing loss

Mutation	**Gene / product**	**Additional features**
rRNA genes		
A1555G	MTRNR1 / 12s rRNA	
A827G	MTRNR1 / 12s rRNA	
T961delT/insC	MTRNR1 / 12s rRNA	
T961G	MTRNR1 /12s rRNA	
T1095C	MTRNR1 / 12s rRNA	
tRNA genes		
A3243G	MTTL1 / $tRNA^{leu(UUR)}$	MIDD, MELAS, PEO
T3271C	MTTL1 / $tRNA^{leu(UUR)}$	MIDD
A4269G	MTTI / $tRNA^{Ile}$	Cardiomyopathy

A4336G	MTTQ / $tRNA^{Gln}$	Migraine
T4336C	MTTQ / $tRNA^{Gln}$	Alzheimer, Parkinson, Migraine
A7445G (T7445C)	MTTS1 / $tRNA^{Ser(UCN)}$	PPK
7472insC	MTTS1 / $tRNA^{Ser(UCN)}$	Ataxia, Dysarthria, Myoclonus
T12201C	$tRNA^{His}$	Nonsyndromic hearing loss
G5821A	$tRNA^{Cys}$	Aminoglycoside-induced and nonsyndromic hearing loss
T15908C	$tRNA^{Thr}$	Aminoglycoside-induced and nonsyndromic hearing loss
G8363A	tRNALys	Maternally inherited cardiomyopathy, Deafness, Autism, Myoclonic epilepsy and ragged red fibers
Protein-coding genes		
A7443G	MTCO1 / Cox1	
G7444A	MTCO1 / Cox1	
A8108G	MTCO2 / Cox2	
A13513G	MTND5	MELAS
G8078A	MTCO2	
Mitochondrial D-loop		
A263G	HVII	
T310C	HVII	

KSS, Kearns-Sayre syndrome; MELAS, myoclonic epilepsy, lactic acidosis, and stroke-like syndrome, MIDD, maternally inherited diabetes and deafness; PEO, progressive external ophthalmoplegia; PPK, palmoplantar keratoderma; rRNA, ribosomal RNA; tRNA, transfer RNA.

4.8. Conclusion

mtDNA mutations have been associated to hearing and balance failure. Genetic analysis would benefit patients and their relatives if they were being offered counselling and preventive strategies. However, as long as the cochlea is inaccessible to biological studies, it remains unclear why it is so dependent on mitochondrial functioning. A deeper understanding of the basic biology of mitochondria holds promise for developing effective therapies for patients with hearing impairment, which currently remain at the level of palliative and symptomatic approaches.

Chapter five: Discussion and future directions

5.1. Linking statements from manuscripts

The previous manuscript reviewed the mitochondrial mutations that are known to result in presbyacusis. Whether these mutations result in presbyastasis, or whether other new mutations are responsible for it would be a topic of interest, because it will add to the benefits of using hearing aids. If so, individuals who have hearing loss would be counseled that using their hearing aids would not only help them hear better and preserve their hearing, but also hearing aids would improve their awareness in various environments, and this would help them maintain their postural stability and should help them to avoid falls.

5.2. Future directions

A clinical study for different age groups of hearing aid users should compare (a) hearing aid users who do not suffer from balance disorders with (b) hearing aid users who have balance disorders. Balance tests should be performed and mtDNA data should be collected. Results could then be compared in individuals with presbyastasis in order to detect any mtDNA that could result in both presbyacusis and presbyastasis. The mechanism(s) with which this particular mutation or mutations might result in damage to the inner ear should then be investigated.

Chapter six: Overall Conclusion

6.1. Conclusion

The broad vision that motivated the work in this thesis was to revisit the interaction between hearing and balance and to investigate this interaction under various conditions, with a focus on the effect of hearing loss on balance. The increased incidence of falls and their consequent financial and health burdens warranted this investigation, particularly with the emergence of new reports that suggested that the benefits of hearing aids might extend to balance preservation. The first manuscript showed that although cochlear implant surgery can affect the results of various vestibular tests, the clinical effect is tolerable by patients in most cases. However, it also showed that a considerable percentage of cochlear implant candidates have abnormal vestibular test results before the surgery. The clinical study presented in the second manuscript found that providing auditory inputs and using hearing aids can improve postural stability in individuals with hearing loss. It also suggested that age might play an important role in addition to the degree of hearing loss in postural stability. This observation was the motivation to conduct a review of the possible mitochondrial DNA mutations that might result in hearing loss with age and suggested the possibility that these mutations might be responsible for presbyastasis as well as presbyacusis.

6.2. Claims of originality

This thesis investigated the interaction between hearing and balance in various contexts.

The first manuscript is the first study to provide a meta-analysis to quantify the potential deterioration in postural stability and vestibular function tests after cochlear implant surgery. It was found that CI surgery could significantly affect the results of caloric, as well as VEMP testing. However, no significant effect was detected in HIT results, posturography, or DHI scores. Variability among patient populations, pre-existing conditions, as well as measurement and reporting differences made it difficult to draw a definitive conclusion. Age and etiology of

hearing loss appeared to affect vestibular function after CI surgery. Nonetheless, the possible effects of CI surgery on the vestibular system should be communicated to CI recipients before surgery.

The second manuscript presents the first clinical study to compare postural stability of normal hearing individuals and of hearing aid users. It was found that auditory input does not seem to affect postural stability of normal hearing levels. However, hearing aid users showed a significant improvement in postural stability in the presence of auditory inputs, as well as an improvement in their sound localization abilities. No association between the ability to localize sounds and postural stability was found.

The third manuscript presents an updated review (i) of mitochondrial mutations that are known to result in hearing loss with age (presbyacusis), and (ii) of whether presbyastasis can also be partly attributed to mitochondrial dysfunction. This review showed that mtDNA mutations have been associated to hearing and - potentially – to balance failure. This association is further supported by the results of the second manuscript where both aging and hearing loss were associated with a deterioration in balance. Together these results suggest that genetic analysis would benefit patients and their relatives if they were offered counselling and preventive strategies. However, as long as the cochlea is inaccessible to biological studies, it remains unclear why it is so dependent on mitochondrial functioning. A deeper understanding of the basic biology of mitochondria holds promise for the development of effective therapies for patients with hearing impairment, which currently remain at the level of palliative and symptomatic approaches.

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