

**A Demographic and Electrocochleographic Study of  
Ménière's Disease and Migraine Vertigo**

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By

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## Abstract

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Ménière's disease (MD) is an inner ear condition characterised by progressive hearing loss, tinnitus, aural fullness, and vertigo. Migraine is a common, chronic neurovascular disorder characterised by attacks of severe headaches, autonomic nervous system dysfunction, and, in some patients, visual disturbances. Patients with certain subclasses of migraine may also present with symptoms typically experienced by MD sufferers, such as vertigo, hearing loss, and tinnitus. Currently most MD cases are diagnosed through subjective criteria such as the guidelines provided by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing Equilibrium (AAO-HNS CHE) and the Gibson score. Migraine is diagnosed subjectively according to the International Headache Society (IHS). The purpose of this study was to investigate whether tone burst Electrocochleography (ECoChG) measures, which have been found to be effective in assisting with the diagnosis of MD, may be sensitive in differentiating between suspected MD patients with and without a history of migraine. A database of 395 patients, whose medical files included ECoChG records, was analysed. The ECoChG data and other patient characteristics were compared between three groups, including patients who had a history of migraine and attacks of vertigo ("Migraine"), patients who had no history of migraine but reported having had headaches and attacks of vertigo ("No migraine-with headache"), and patients who reported having had attacks of vertigo but neither a history of migraine nor headaches ("No migraine-without headache"). The "Migraine" group was found to have a significantly higher proportion of "negative" ECoChG cases compared to the other two groups. The "Migraine" group also had the lowest occurrence of hearing loss and lowest mean Gibson scores amongst the three groups. These findings suggest that some patients who are subjectively diagnosed with MD may have vestibular migraine instead of MD. It is, therefore, concluded that utilisation of physiological test such as ECoChG may improve the differential diagnosis of MD and vestibular migraine.



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# Chapter One: Introduction

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This study investigates whether tone-burst electrocochleography (ECochG) may assist in the differential diagnosis of Ménière's disease (MD) and migraine patients who suffer from vertigo. This chapter provides an overview of the rationale for the investigation and a literature review on MD, migraine and vestibular migraine, subjective and physiological assessments used in the diagnosis of MD and migraine, and treatment of MD and migraine. The importance of the research question and the aims and hypotheses of the study are also described.

## 1.1. Overview

Progressive hearing loss, tinnitus, aural fullness, and attacks of rotary vertigo characterize MD, an inner ear disease first described by French physician Prosper Ménière in 1861 (Ménière, 1861, cited in Sajjadi & Paparella, 2008; Semaan & Megerian, 2011). Ménière's disease is a relatively common disorder, with a prevalence rate ranging from 17 to 513 individuals per 100,000 (Havia, Kentala, & Pyykkö, 2005; Radtke et al., 2008; Watanabe et al., 1995; Wladislavosky-Waserman, Facer, Mokri, & Kurland, 1982). The progressive hearing loss associated with MD occurs unilaterally or bilaterally and typically starts at low frequencies and progresses to high frequencies resulting in a characteristic peaked audiogram configuration (Vrabec, Simon, & Coker, 2007). Patients typically experience Ménière's symptoms in clusters, with periods of severe vertigo and aural symptoms followed by asymptomatic periods (Ibekwe & Ijaduola, 2007). As MD is associated with fluctuating symptoms which are also shared by other medical conditions, the diagnosis of MD can be challenging.

Vertigo, one of the symptoms leading to MD, is a sensation of dizziness indicating a problem in the vestibular pathway (Phillips, Longridge, Mallinson, & Robinson, 2010). Patients with MD experience rotary vertigo which usually lasts for several hours although the attack may last between 20 minutes and a day (Huppert, Strupp, & Brandt, 2010). The most common peripherally based vertigo, which is caused by a mechanical malfunction of the inner ear, is benign paroxysmal positional vertigo (Uneri, 2004). Patients with benign paroxysmal positional vertigo (BPPV) have rotary vertigo similar to that experienced by MD patients; however, in BPPV, vertigo lasts for seconds and is elicited by position changes of the head. Both paroxysmal positional vertigo and MD, as well as episodic vertigo, have been found to be more prevalent in patients with migraine than in those without (Uneri, 2004; Cha & Baloh, 2007).

Migraine is a neurovascular disorder characterised by sporadic attacks of head pain. Some variations in the manifestation of migraine across different pathologies have also been observed. For example, it has been reported that while individuals with MD tend to experience a brief bout of migraine, those with migraine-associated vertigo (termed “migraine vertigo”) may have a migraine lasting more than 24 hours (Strupp, Versino, & Brandt, 2011). As for migraine without vertigo, it may be more related to problems in the central vestibular pathway or the neurovascular or neurochemical abnormality associated with affective disorders (Merikangas, Angst, & Isler, 1990). A strong link between vertigo and migraine has been reported (Lempert, Neuhaser, & Daroff, 2009) and the relationship between these two disorders is complex. Although some subtle differences in the presentation of symptoms may be useful for formulating a tentative clinical diagnosis of MD based on subjective symptoms alone, the fluctuating symptoms associated with MD render difficulty in confirming the differentiation between MD and migraine vertigo.

Some publications including Menière's 1861 paper (as cited in Gopen, Viirre, & Anderson, 2009) have reported an association between MD and migraine (Kayhan & Hood, 1984; Parker, 1995; Radtke et al., 2008; Gopen et al., 2009). Patients with certain sub-varieties of migraine also commonly experience aural aura, such as hearing a buzzing sound, prior to the migraine, as well as nausea, vomiting, and increasing sensitivity to light, sound, and smell. Several epidemiological studies have demonstrated a greater-than-chance rate of comorbidity between MD and migraine, leading some authors to conclude that an association exists between MD and migraine (Ibekwe et al., 2008; Radtke et al., 2008). Other studies, however, suggest that migraine and MD are unrelated disorders (Rassekh & Harker, 1992; Gopen et al., 2009) and propose that the high rate of comorbidity between MD and migraine may be attributable to a vertigo sub-variety of migraine called vestibular migraine (Lempert et al., 2009). Vestibular migraine is characterised by acute attacks of vertigo which are often with associated migrainous symptoms such as aura and hypersensitivity. Vestibular migraine typically presents in patients with a history of migraine (Lempert et al., 2009). In general, the majority of clinicians use subjective measures rather than objective measures for the diagnosis of MD. It is possible that a proportion of patients with MD-like symptoms and migraine may have a vertigo sub-variety of migraine, known as vestibular migraine. The use of subjective diagnostic methods may lead to a greater proportion of vestibular migraine patients being misdiagnosed with MD.

Extensive etiological studies have shown that endolymphatic hydrops, the distention of scala media within the cochlea, forms the pathophysiologic basis of MD (Hall, 2007; Hallpike & Cairns, 1938). Although the exact mechanism is disputed, it is often postulated that endolymphatic hydrops is probably related to the endolymphatic sac being unable to clear excess endolymph from scala media (Hornibrook, George, Spellerberg, & Gourley, 2011). Surgical and

medical treatments of MD, therefore, often focus on reducing the distension of scala media and decreasing endolymphatic hydrops (Carey, 2010). The diagnosis of MD remains challenging for the clinician as endolymphatic hydrops cannot be confirmed in vivo. Consequently, a range of subjective and physiological measures are employed to improve the accuracy of the diagnosis of MD (Fiorino, Pizzini, Beltramello, & Barbieri, 2011; Kalin, 2010). Subjective assessments can be defined as measures where the impression or opinion of the assessor determines the score. Criteria based on the clinical guidelines provided by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing Equilibrium (AAO-HNS CHE) and Gibson score are commonly used in the diagnosis of MD. Despite the fact that AAO-HNS CHE and Gibson score are considered useful diagnostic tools, objective physiological assessments of MD are required for a comprehensive diagnosis (Kalin, 2010; Nguyen, Harris & Nguyen, 2010). Objective assessments currently available for the diagnosis of MD mainly include (1) ECoChG testing, which assesses the responsiveness of the inner ear hair cells, (2) vestibular evoked myogenic potential (VEMP) testing, which assesses saccule dysfunction, (3) a new auditory brainstem response (ABR) technique called cochlear hydrops analysis masking procedure (CHAMP), which tests for cochlear hydrops (Adams, Heidenreich, & Kileny, 2010; De Valck, Claes, Wuyts & Van de Heyning, 2007), and (4) magnetic resonance imaging (MRI), which is a medical imaging technique that can be used to visualize endolymphatic hydrops (Fiorino, et al., 2011). Amongst these objective physiological methods, ECoChG is most widely investigated in the literature and has been considered to have the most potential for development as a standard clinical tool for the diagnosis of MD (Saeed, 1998).

Electrocochleography is an electrophysiological technique where auditory evoked responses are measured from the surface of the promontory inside the middle ear cavity. Clicks

and tone bursts presented to patients at varying intensity levels evoke electrical potentials of the inner ear. The outcome of the ECochG can be calculated from the ratio of the summing potential to the action potential of the response waveform or the absolute measurement of the summing potential at different frequencies (Gibson, 1996). Due to the overlap of some MD and vestibular migraine symptoms, reaching a differential diagnosis using only information from case history is likely to be challenging in some cases. In such patients, an objective test such as ECochG may assist in the differential diagnosis (Gopen et al., 2009). Measures from ECochG waveforms have been found to be sensitive to changes in hair cell position caused by endolymphatic hydrops, which are usually present in patients with MD. Therefore, the usefulness of ECochG in the differentiation between MD and vestibular migraine is determined by whether vestibular migraine has an underlying pathophysiology unrelated to endolymphatic hydrops.

## **1.2 Literature Review**

This literature review provides information on topics related to MD, migraine, vestibular migraine, subjective and physiological assessment of MD, and the treatment of MD and migraine.

### **1.2.1 Ménière's Disease**

This section provides a review on the literature of MD, starting from the historical background of MD, followed by current understanding of the epidemiology of MD, pathophysiological theories of MD, and the clinical presentation of MD.

### *1.2.1.1 Historical Background*

In 1861, Prosper Menière presented a series of papers before the French Academy of Medicine, providing a description of the disease that now bears his name (Ruckenstein, 2010). Based on clinical observations and findings in previous experiments, Menière concluded that the main clinical symptoms of MD were vertigo attacks, tinnitus, and progressive hearing loss, and the likely cause was a lesion of the semicircular canals. As the director of a large Parisian deaf and mute institute, Menière had observed many patients with vertigo, hearing loss, and tinnitus. These observations, along with findings from research carried out by the physiologist Marie Jean Pierre Flourens on pigeons, lead to Menière's conclusion that vertigo can originate from the inner ear. Flourens's experiment conducted on pigeons showed that surgical damage to the semicircular canals resulted in balance disturbance, with the bird's head and body orienting in the direction of the damaged semicircular canals. Menière's papers initially caused great controversy at the French Academy of Medicine, as the role the inner ear plays in balance was completely unknown at the time of the publication (Baloh, 2001; Flourens, 1824, cited in Baloh, 2001). The next landmark paper was published by Hallpike and Cairns (1938), who coined the term "endolymphatic hydrops" to describe the swelling of scala media in patients with MD. Hallpike and Cairns used their histologic observations of the temporal bone of post-mortem MD patients to infer the pathophysiological basis of MD (Hallpike & Cairns, 1938). In 1966, Klockhoff and Lindblom combined their knowledge of endolymphatic hydrops and osmotic diuretics to develop the glycerol dehydration test for MD. The test involves baseline and post-glycerol-ingestion audiometry to determine whether glycerol injection helps improve hearing thresholds by decreasing endolymphatic hydrops. Although no longer used routinely due to the impracticality of the test, the glycerol dehydration test supports the theory that endolymphatic

hydrops is caused by the overproduction or impaired absorption of endolymph. The psychoacoustic phenomenon of loudness recruitment has also been used to support the diagnosis of MD. Hallpike and Hood (1959) found, in a study of 200 patients with MD symptoms, that all of these patients experienced abnormal growth of perceived loudness with increasing stimulus intensity. Although loudness recruitment testing, which compares the patient's perception of stimulus loudness between ears, has been shown to have high sensitivity for MD, its specificity is poor with numerous other cochlear pathologies exhibiting this phenomenon. Loudness recruitment testing is no longer regularly performed primarily because of its low specificity, but also due to the time consuming nature of the test (Adams et al., 2010). To assist in the diagnosis of MD, a variety of subjective and objective assessment tools have been developed as will be described in Sections 1.2.3 ("Subjective Assessments") and 1.2.4 ("Physiological Assessments").

#### *1.2.1.2 Epidemiology*

This section provides a review of the epidemiologic attributes of MD patients, including the prevalence, incidence, age, gender, and ethnicity of patients with MD.

##### *1.2.1.2.1 Prevalence and Incidence*

The prevalence and incidence data on MD vary widely between studies. Estimates of MD prevalence, which is the number of cases present in a given population at a certain time, range from 17 to 513 individuals per 100,000 (Havia et al., 2005; Watanabe et al., 1995; Wladislavosky-Waserman et al., 1982). Estimates of MD incidence, which is the number of new cases in a given population during a certain time period, range from 5 to 46 individuals per 100,000 people per year (Biagini, Nuti, & Sensini, 1991, cited in Ruckenstein, 2010; Celestino & Ralli, 1991; Watanabe et al., 1995; Wladislavosky-Waserman et al., 1982). These wide

variations in reported prevalence and incidence can be attributed to the use of subjective measures, methodological differences, differences in sample population, and changes to the diagnostic guidelines over time (Harris & Alexander, 2010). The original AAO-HNS guidelines (1972) specified distinct cochlear and vestibular variants of MD whilst the 1985 and 1995 guidelines excluded these variants and included classical MD only. The Ménière's Disease Research Committee of Japan also published, in 1976, a diagnostic criterion, which was later modified by the Japanese Society for Equilibrium Research (JSER) in 1988 (Shojaku et al., 2009). Using the 1972 AAO-HNS CHE approach, Wladislavosky-Waserman et al. (1984) published an epidemiological study for MD using data that spanned 30 years for the population of Rochester, Minnesota. The incidence was estimated to be 15.3 per 100,000 people per year and the prevalence was estimated to be 218.2 per 100,000 people (Wladislavosky-Waserman et al., 1984). More recently, Shojaku et al. (2005) conducted a retrospective survey using the 1995 AAO-HNS criteria and found a prevalence of 43.5 per 100,000 and an incidence of 5 per 100,000 in a Japanese district. Havia et al. (2005) used the 1988 JSER criteria and found a much higher prevalence of 513 per 100,000 in southern Finland. In 1991, a relatively high MD incidence of 27.5 per 100 000 was published by Biagini et al. (as cited in Ruckenstein, 2010) following a 10 year study in Siena, Italy. As a range of different diagnostic criteria were used in these studies, greater adherence to guidelines and test protocols may help enhance the comparability and usefulness of the prevalence and incidence data in future epidemiological studies. The use of a physiological assessment to objectively calculate the prevalence of MD may also improve the accuracy of the estimations.

#### *1.2.1.2.2 Age*

The most common age of onset for MD symptoms is uncertain as estimations from previous research have been highly variable. The majority of papers suggest the onset is most common in middle aged people in their fourth or fifth decade of life (Paparella, da Costa, Fox & Yoo, 1991). Recent research suggests that the incidence of MD is also common in older individuals (Shojaku et al., 2009). Shojaku et al. (2009) conducted four nationwide surveys of MD in Japan from 1975 to 2006 and found in their most recent survey, which was conducted from 2001 to 2006, that definite MD onset was most common for men in their fifth decade of life and for women in their sixth decade of life. The authors took the different age distributions in Japan at the time of the surveys into account by using denominators interpolated from census data to remove any age bias from the results. Similar findings have also been published by Havia et al. (2005) and in an early publication by Wladislavosky-Waserman et al. (1984). Shojaku et al. (2009) postulated that the shift of the peak age of incidence toward an older age in recent years may be due to increased stress among elderly people. Increased health from modern medicine may be causing people to pursue their careers for a longer period of time, leading to job-related and physiologic stress, which has been linked by some researchers to MD. It is important to note that MD is rarely found in children. In 1987, Hausler, Toupet, Guidetti, Basseres and Montandon (cited in Choung, Park, Kim, Kim, & Kim, 2006) found that, out of 598 children who complained of dizziness, only nine children received a diagnosis of MD. These studies suggest that although MD onset is common between the ages 40 and 50 years, MD can occur at any age and MD onset may be becoming increasingly common in people aged between 50 and 60 years.

**Table 1.** Publications on age of patients with MD.

| Publication                          | Population     | Methods   | Finding                                 |
|--------------------------------------|----------------|---|---|
| Ibekwe & Ijaduloa (2007)             | West African   | Retrospective hospital records (n = 11,463)         | Average study population age = 47.2 yrs |
| Havia et al. (2005)                  | Finland        | Questionnaire (n = 3,116)                           | Average study population age = 45 yrs   |
| Wladislavosky-Waserman et al. (1984) | Rochester, USA | Retrospective hospital records (n = 1,164)          | Average onset age = 50 yrs              |
| Celestino & Ralli, (1991)            | Latium, Italy  | Twelve-year prospective hospital study (n = 12,150) | Average study population age = 48 yrs   |

#### *1.2.1.2.3 Gender*

A number of studies have indicated a slight bias towards females being affected by MD; however, many other studies have shown that males and females have a similar chance of developing MD. Havia et al. (2005) found, in southern Finland, that women had a higher likelihood of being afflicted with MD than men, with the prevalence of MD in women reported to be 742 per 100,000 while that for men to be smaller at 222 cases per 100,000. However, the male response rate was low (43%) in Havia et al.'s (2005) study and thus the generalizability of this finding may be questionable. In a retrospective survey of 375 patients from Nishikubiki, Japan, Shojaku et al. (2005) also found that more females were affected in two distinct populations they surveyed. In contrast to these findings, earlier research by Wladislavosky-Waserman et al. (1984) and Celestino & Ralli (1991) showed that there was no statistically

significant difference between the number of males and females affected by MD. In summary, although no gender difference in the prevalence of MD was shown in the past, women were found to be at a higher risk of having MD in more recent studies.

**Table 2.** Publications on gender ratio of patients with MD

| Publication                          | Population         | Methods   | Finding                            |
|--------------------------------------|--------------------|---|------------------------------------|
| Celestino & Ralli, (1991)            | Latium, Italy      | Twelve-year prospective hospital study (n = 12,150) | ~1:1 (not significantly different) |
| Havia et al. (2005)                  | Finland            | Questionnaire (n = 3,116)                           | ~2:1 (females: males)              |
| Wladislavosky-Waserman et al. (1984) | Rochester, USA     | Retrospective hospital records (n = 1,164)          | ~1:1 (not significantly different) |
| Shojaku et al. (2005)                | Nishikubiki, Japan | Retrospective survey (n = 375)                      | ~1.5:1 (females: males)            |

#### 1.2.1.2.4 Ethnicity

Epidemiological studies of MD have been most prevalent in Europe and America and, as a result, most of the available epidemiological literature is from patients of Caucasian ethnicity. Although many studies on the prevalence of MD in Caucasians populations have been published, a consensus on epidemiological data has yet to be reached (see Table 3). A review of four studies on Caucasians people revealed that estimations of MD prevalence range widely from 43 to 513 per 100,000 individuals. The various data sources of these studies included an insurance database, hospital records, and a set of questionnaire responses (Harris & Alexander, 2010;

Havia et al., 2005; Kotimäki, Sorri, Aantaa, & Nuutinen, 1999; Wladislavosky-Waserman et al., 1984). A number of publications have also come from Japan, showing that Japanese patients have a slightly lower prevalence of MD when compared to the findings from Europe and American MD studies. For example, Shojaku et al. (2005) conducted two retrospective studies of Japanese districts Nishikubiki and Toyama and estimated a lower average prevalence than found in any of the studies on Caucasians. The first epidemiologic study of MD patients in Africa was published in 2007 and revealed a relatively high retrospective prevalence, which was within the wide range of estimations published in Caucasian studies (Ibekwe & Ijaduloa, 2007). In the literature, epidemiologic data on MD are highly variable between studies regardless of the race of the patients. The methodology used in epidemiological studies needs to become more standardized to allow the detection of any differences between ethnicities.

**Table 3.** Publication on the MD prevalence of different ethnic groups

| Publication               | Population   | Methods                                 | Finding         |
|---------------------------|--------------|---|-----------------|
| Ibekwe & Ijaduloa (2007)  | West African | Retrospective hospital records          | 220 per 100,000 |
| Harris & Alexander (2010) | USA          | Health insurance database (n = 473,000) | 190 per 100,000 |
| Havia et al. (2005)       | Finland      | Questionnaire                           | 513 per 100,000 |

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|                                      |  |                                |                   |
|--------------------------------------|--|--------------------------------|-------------------|
| Kotimäki et al. (1999)               | Finland                                  | Retrospective hospital records | 43 per 100,000    |
| Shojaku et al. (2005)                | Nishikubiki and Toyama Prefecture, Japan | Retrospective surveys          | 34.5 per 100,000  |
| Wladislavosky-Waserman et al. (1984) | Rochester, USA                           | Retrospective hospital records | 218.2 per 100,000 |
| Watanabe et al. (1995)               | Toyama Prefecture, Japan                 | Survey                         | 17 per 100,000    |

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### *1.2.1.3 Pathophysiology*

Post-mortem histopathology examinations of human temporal bones carried out by Hallpike and Cairns (1938) and Yamakawa (1938) more than 70 years ago formed the basis of our current understanding of the pathophysiology of MD. Hallpike and Cairns (1938) observed signs of distension of the endolymph system in the temporal bones of post-mortem MD patients and used the term “endolymphatic hydrops” to describe the swelling of scala media within the cochlea. However, many later studies have shown that endolymphatic hydrops can frequently occur without symptoms of MD and is sometimes seen with other auditory related pathologies including otitis media, meningitis, otosclerosis, and head trauma (Merchant, Rauch & Nadol,

2005; Paparella, 1991). This has led to uncertainty about the association between MD and endolymphatic hydrops and caused authors to caution against using the terms MD and endolymphatic hydrops synonymously (Ruckenstein, 2010). Furthermore, some authors have suggested that endolymphatic hydrops may simply be an epiphenomenon of the, yet to be revealed, true pathophysiology of MD (Merchant et al., 2005).

Several theories have been postulated to explain how endolymphatic hydrops develops and causes the characteristic symptoms of MD. The rupture theory proposed by Schucknect and Ruther (1991) suggests that the symptoms of MD are caused by an electrical imbalance which occurs when Reissner's membrane ruptures allowing the perilymph and endolymph to mix together. According to Schucknect and Ruther (1991), a fibrosis (abnormal fibrous tissue) within the endolymphatic duct results in the obstruction which causes the hydrops and consequential rupturing. It is hypothesised that patients with MD experience a sudden onset of symptoms while the Reissner's membrane rapidly repairs itself. This theory was challenged by McNeill, Cohen and Gibson (2009), who showed that patients with MD experienced no significant changes to audiometric thresholds during attacks of vertigo and argued that the intact audiometric threshold was indicative of an intact cochlear function and thus an intact Reissner's membrane. The drainage theory proposes that the normal mechanism for gradual longitudinal drainage of endolymph towards the endolymphatic sac is damaged in MD patients (Gibson, 1996). It is hypothesised that accumulation of endolymph in the scala media of MD patients triggers a rush of longitudinal flow of the endolymph causing vertigo (Gibson, 1996). Lastly, the chemical theory postulates that endolymphatic hydrops develops when mechanical stress on the cochlear membranes cause transitory leakages of potassium-rich endolymph into the relatively potassium-poor perilymph of scala tympani (Horner, 1991). The rupture, drainage, and chemical

theories differ in the exact mechanism of how endolymphatic hydrops occurs; however, they agree that an imbalance in endolymph and perilymph is involved.

Ménière's disease is sometimes found to affect multiple family members. Recent studies have suggested that a genetic link may be responsible for 5% of MD cases. Several studies have attempted to find the gene which codes for familial MD; however, a consensus has yet to be reached. A study by Morrison & Johnson (2002) found a linkage to chromosome 14 in affected families while Klar, Frykholm, Friberg, & Dahl (2006) suggested a linkage to chromosome 12p12.3. Genetic information encodes changes to the inner ear physiology of patients with MD, making these patients more susceptible to developing endolymphatic hydrops through the aforementioned mechanisms.

#### *1.2.1.4 Clinical Presentation*

Patients with MD present with a range of different auditory and vestibular symptoms. Studying the symptoms of MD may help in the development of diagnostic tests, selection of appropriate medical intervention, and provision of practical information for patient counselling.

##### *1.2.1.4.1 Symptoms*

Patients with MD classically endure clusters of hearing loss, tinnitus, aural fullness, and repeated vertiginous spells (Sajjadi & Paparella, 2008; Semaan & Megerian, 2011). In the early stages of the disease, the symptoms typically do not occur simultaneously and the first presenting symptom varies between patients (Carey, 2010). A questionnaire-based study by Havia et al. (2005) showed that 61% of MD patients reported experiencing cochlear symptoms (hearing loss, tinnitus, and aural pressure) before vertigo, with 29% of patients identifying hearing loss and 32% identifying tinnitus as their first symptom. Patients with MD may also have an assortment

of secondary symptoms, including nausea and vomiting, hyperacusis (i.e., oversensitivity to sounds at a certain frequency range), recruitment (i.e., intolerance of ordinary sound levels), diplacusis (i.e., perceiving an auditory stimulus as two sounds that are different in pitch), horizontal nystagmus (i.e., involuntary eye movement in a horizontal direction), drop attacks (otolithic crises of Tumarkin), tendency to fall, depression, fatigue, and anxiety (Carey, 2010; Minor, Schessel, & Carey, 2004; Paparella, 1991).

Patients in the early stages of MD typically have a low frequency rising sensorineural hearing loss and often notice fluctuations in their hearing. This differentiates MD from other auditory conditions such as noise exposure, ototoxicity, and presbycusis. In the later stages of the disease, patients with MD usually also experience hearing loss in the high frequencies with preservation in the mid frequencies. This audiometric configuration is called a peaked or “V” audiogram. Patients with MD often present with a slight conductive component to their hearing loss which may cause a misdiagnosis of Eustachian tube dysfunction. Hearing loss caused by MD normally begins to stabilize about 5 years after patients first become symptomatic, with most of the hearing being lost between 5 and 10 years (Huppert et al., 2010). Research has shown that the hearing levels of MD patients stabilize at a flat 50 dB hearing loss. Profound hearing loss, which is very rare in MD cases (1-2%), usually suggests the existence of a second auditory pathology if found in a MD patient (Carey, 2010).

The tinnitus experienced in MD is non-pulsatile and often likened to a low frequency roar. Havia et al. (2002) found that the severity of tinnitus experienced by MD patients varies greatly, with 38% reporting mild tinnitus, 32% reporting moderate tinnitus, and 30% reporting severe tinnitus. Severe tinnitus is reported to occur more often in later stage MD patients. Aural

fullness or pressure in the ear is also experienced in 50% to 70% of MD patients, especially during chronic stages of the disease (Huppert et al., 2010).

Patients with MD characteristically experience an abrupt onset of vertigo attacks. Due to their unpredictability and severity, vertigo attacks are often the most debilitating symptom of MD. The AAO-HNS defines vertigo as “the sensation of motion when no motion is occurring relative to the earth’s gravity”. Patients with MD have been known to describe such symptoms as vertigo, dizziness, or giddiness (Stapleton & Mills, 2008). The attacks of vertigo last at least 20 minutes and can continue for up to 24 hours in duration. Such is the severity of vertigo attacks; patients are frequently admitted to hospital during vertiginous episodes which can begin at any time of the night or day (Carey, 2010). It has been reported that worsening of the cochlear symptoms of tinnitus, aural pressure, and hearing loss commonly precedes the vertigo attack while nausea and vomiting accompany the attack (Carey, 2010). However, a study by McNeill et al. (2009) found no change in audiometric thresholds during vertigo attacks. In the early stages of MD, patients experience approximately 6 to 11 attacks per year. As the condition becomes chronic, the severity and the number of vertigo attacks declines or may completely disappear. A long term follow-up study revealed that after a follow-up of at least 14 years, vertigo had disappeared in 50% of patients and improved in 28% of patients (Green, Blum, & Harner, 1991). The drop attacks experienced by some MD patients may occur early or later in the course of the disease (Huppert et al., 2010).

#### *1.2.1.4.2 Unilateral and Bilateral MD*

Although MD may occur unilaterally or bilaterally, MD patients who eventually develop bilateral MD usually present to medical attention first with unilateral symptoms and then subsequently develop contralateral involvement (Thorp & James, 2005). The occurrence

estimates for bilateral MD are highly variable. For example, Chaves, Boari, and Lei Munhoz (2007) found that 13 of 39 (33.3%) MD patients had bilateral MD while Perez et al. (2004) found in a study of 101 MD patients that only 5% of them had bilateral MD. Histopathological findings from temporal bone studies indicate a much higher incidence of bilateral MD, with 25-30% of MD patients showing evidence of bilateral involvement (Perez, Chen, & Nedzelaki, 2007). The variation in the reported prevalence of bilateral MD is most likely due to the lack of diagnostic guidelines for bilateral MD and the high variability in the duration of the patient follow-up periods (Nabi & Parnes, 2009). Another point of controversy is the timeframe in which contralateral symptoms starts. Some neuro-otologists suggest that bilateral symptoms would be expected to arise within 2 to 5 years following the initial MD symptoms; however, many other researchers dispute this and suggest that the frequency of contralateral involvement increases over time and that there is no timeframe where a MD patient is safe from developing contralateral symptoms (Paparella & Griebie, 1984; Perez et al., 2007). Huppert et al. (2010) recently reviewed 46 studies on the long-term course of MD and concluded that bilateral involvement increases with time, with 35% of MD patients developing bilateral MD in the first 10 years and 47% within 20 years following onset of the first MD sign.

## **1.2.2 Migraine and Vestibular Migraine**

The following section provides a review on the literature of migraine and a subclass of migraine known as vestibular migraine and the association between migraine and MD.

### *1.2.2.1 Background*

Migraine is a neurovascular disease characterised by attacks of head pain with intervening symptom-free periods. Patients with migraine usually report that the head pain is

throbbing, recurrent, and appearing only on one side of the head (unilateral). According to the current International Classification of Headache Disorders (ICHD) of the International Headache Society (IHS, 2004), patients diagnosed as having migraine without aura (formerly known as “common migraine”) may also report associated symptoms of nausea, vomiting, sensitivity to movement, photophobia (aversion to light), phonophobia (a fear of loud sounds), and osmophobia (hypersensitivity to odours). One IHS recognised diagnosis called “migraine with aura” (formerly known as “classical migraine”) refers to the type of migraine with episodes preceded by transient focal neurologic signs such as visual auras (Goadsby, Lipton, & Ferrari, 2002). Attacks of migraine with or without aura may be brought on by exposure to patient-specific migraine-triggers and, if left untreated, usually last between 4 to 72 hours (Goadsby et al., 2002). The IHS uses a hierarchical classification system to organize 18 distinct migraine sub-types into seven broader categories of migraine including: migraine without aura, migraine with aura, childhood periodic syndromes that are commonly precursors of migraine, retinal migraine, complications of migraine, migraine-triggered seizure, and probable migraine (Headache Classification Committee, 2004).

Although vestibular migraine does not currently fit into the 2004 IHS diagnostic criteria, the notion that migraine and vestibular symptoms are associated has been gaining acceptance among otologists since the mid 1990s (Millen, Schnurr, & Schnurr, 2011). The term “vestibular migraine” was used to describe patients who experience episodes of vertigo and migraine (Fotuhi, Glaun, Quan, & Sofare, 2009). Other labels for this condition include migraine-associated vertigo, migraine-associated dizziness, and migrainous vertigo (Lempert et al., 2009). Patients with vestibular migraine experience acute episodes of spontaneous or positional vertigo which may last from seconds to days. During these acute vertigo attacks, migrainous symptoms

such as photophobia, phonophobia, osmophobia, and auras may be present while headaches are often absent (Lempert et al., 2009). Most authors agree that hearing loss and tinnitus are not symptoms of vestibular migraine except that some patients may present with fluctuating hearing loss which is usually mild and non-progressive (Johnson, 1998). Vestibular migraine can occur at any age. Many patients suffer from migrainous episodes many years prior to the manifestation of vestibular migraine, with some patients reporting decades of symptom-free years in-between (Dieterich & Brandt, 1999; Neuhauser, Leopold, von Breven, Arnold, & Lempert, 2001). Vestibular migraine attacks follow an irregular pattern of occurrence with episodes being days, months, or even years apart.

#### *1.2.2.2 Epidemiology*

Like migraine, which is more common in females than in males, with a female-to-male ratio of 2 (or 3) to 1 (Rasmussen, 2001), vestibular migraine also has a high female-to-male ratio, which ranges between 1.5 to 1 and 5 to 1 (Neuhauser & Lempert, 2004). Migraine and vertigo are both relatively common disorders. The reported lifetime prevalence of migraine is approximately 14% in the general population while a lifetime prevalence of 7% has been reported for vestibular vertigo (Jenson & Stovner, 2008; Neuhauser and Lempert, 2009). A large population study by Neuhauser et al. (2006) estimated that 3.2% of the general population experience both migraine and vestibular vertigo over their lifetime. The high rate of comorbidity between migraine and vertigo has been explained in two ways: 1) Individuals with migraine have a higher predisposition for MD or another vertigo syndrome and 2) Migraine and vertigo are the two characteristic symptoms of vestibular migraine (Lempert et al., 2009). Theories of the pathophysiology of migraine are reviewed in the following section.

### *1.2.2.3 Pathophysiology*

Three major theories have been proposed to explain the pathophysiology of migraine; vascular, neurological, and dural inflammation. According to the theory of vascular mechanism, migraine is caused by cerebral vasodilatation, which is the dilation of cerebral blood vessels. In contrast, the theory of neurological mechanism proposes that cortical spread of depression, which refers to a wave of inhibition that follows electrophysiological hyperactivity, gives rise to migraine symptoms. Cortical depression is thought to set off a chain of effects starting with the activation of peripheral neurons and meningeal vessels, which in turn activates the central neurons responsible for central sensitization (Millen et al., 2011). Lastly, neurological dural inflammation may cause a migraine through the release of inflammatory neuropeptides (Arulmozhi, Verranjaneyulu, & Bodhankar, 2005). A range of precipitating factors, including diet, sleep deprivation, stress, bright light, and hormonal changes, are known to trigger a migraine in susceptible patients. There are many subcategories of migraine which are likely to have distinct pathophysiologies.

The cause of vestibular migraine is not currently known, although there is likely to be a genetic basis to the disorder. Quite a few authors have proposed theories for the aetiology. It is thought that vestibular migraine attacks may be caused by the cortical spreading of depression as described above for migraine patients (von Brevern, Zeise, Neuhauser, Clarke, & Lempert, 2005). Another theory is that a unilateral release of the chemical transmitters involved in migraine and vestibular neuron activity in the brain causes a vestibular imbalance leading to vertigo (Cutrer & Baloh, 1992). Marano et al. (2005) recorded nystagmus (spontaneous ocular movements) in response to trigeminal activation via electrical stimulation of the forehead and found that migraine patients have significantly lower thresholds for within-the-brainstem crosstalk

compared to controls. This finding suggests that the connections between the trigeminal and vestibular nuclei may play an important role in the aetiology of vestibular migraine. Finally, Murofushi, Ozeki, Inoue, and Sadkata (2009) studied the vestibular-evoked myogenic potentials (VEMPs) of patients with MD and those with vestibular migraine and concluded that they may share a common pathophysiology. They proposed that inflammation of the trigeminal nerve endings in the inner ear may mediate changes in the inner ear resulting in endolymphatic hydrops in patients with vestibular migraine. Murofushi et al. (2009) also cited a publication by Taguguci et al. (2007), who found a nociceptive receptor (TRPV1) related to migraine in the endolymphatic sac (Murofushi et al., 2009). The aetiology of vestibular migraine is currently not well understood; however, apart from Murofushi et al. (2009), who suggested that MD and vestibular migraine might share a common pathophysiology, the majority of findings from studies suggest that the pathophysiology of vestibular migraine is unrelated to endolymphatic hydrops and MD.

#### *1.2.2.4 Association between Migraine and MD*

The proposed association between migraine and MD, which started with observations made by Prosper Menière over 150 years ago (as cited in Gopen et al., 2009), has experienced resurgence in popularity in recent years, with some researchers attempting to identify a physiological link between the two disorders (Kayam & Hood, 1984; Parker, 1995; Cha, Kane, & Baloh, 2007; Radtke et al., 2008; Gopen et al., 2009; Baier & Dieterich, 2009). Although many publications have shown that the frequency of migraine is higher in MD patients compared with the general population, the proposed association between MD and migraine is a contentious aspect of MD research. Radtke et al. (2002) used a telephone questionnaire to compare a group of 78 MD patients with a gender- and age-matched control group and found

that the frequency of migraine was twice as high in the MD patients. In contrast, there is a school of thought that migraine and MD are distinct, unrelated disorders (Rassekh, 1992). An epidemiological study by Gopen et al. (2009) using data from the National Health Interview Survey (NHIS) showed that migraine was not substantially elevated in MD patients compared to the general population. The conflicting findings may have resulted from the methodological differences in the diagnosis of MD.

It is noteworthy that in Radtke et al.'s (2002) study, as well as many other studies in the MD literature, the diagnosis of MD is solely based on the patient's description of symptoms and the clinician's judgment. Since patient descriptions are often difficult to interpret in an objective manner, the diagnosis of MD is challenging. Subjective assessments are frequently used to diagnose MD because of the recommendations of the AAO-HNS CHE guidelines as well as the lack of an absolute biological marker for migraine and MD. The development of a physiological test battery which includes tests such as ECoG and MRI may improve the ability of physicians to objectively differentiate between vertigo caused by MD and migraine generated vertigo (Lempert et al., 2009). A clear differential diagnosis would greatly improve the diagnosis and treatment of both MD and migraine as the management options are different for the two disorders (Shepard, 2006; Gopen et al., 2009).

### **1.2.3 Subjective Assessment**

Subjective assessments can be defined as measures where the impression or opinion of the assessor determines the score. Criteria based on the clinical guidelines provided by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing Equilibrium (AAO-HNS CHE) and the Gibson score are commonly used in the assessment of individuals with MD symptoms. The AAO-HNS CHE guidelines and the Gibson score are

commonly used in isolation or in combination with an instrumental assessment such as ECoChG to diagnose MD. As there is presently no gold standard for the diagnosis of MD, many clinicians rely solely on subjective assessments of clinical history and other clinical features to make their diagnosis.

#### *1.2.3.1 AAO-HNS CHE Criteria*

Symptoms of recurrent spontaneous vertigo, hearing loss, tinnitus, aural pressure, as well as objective documentation of hearing thresholds and otologic examination to exclude other potential causes, are considered in the AAO-NHS CHE criteria (Adams et al., 2010). The AAO-NHS CHE guidelines were first published in 1972 with the aim of improving the reporting of disease outcomes and to provide a consistent method for assigning a diagnosis and classifying MD. The AAO-NHS CHE guidelines were later refined in 1985 and 1995 in accordance with the changing approach of AAO-NHS CHE following advancements in the understanding of MD (Committee on Hearing and Equilibrium, 1972; Committee on Hearing and Equilibrium, 1985; Members of the Committee on Hearing and Equilibrium, 1995). Although the AAO-HNS CHE have updated their guideline on two occasions, some researchers have argued that the guidelines have not progressed enough as they have not incorporated an objective diagnostic test into the guidelines.

Under the current 1995 edition of the AAO-NHS CHE guidelines, a patient can be diagnosed with “possible” MD if they have had an episode of Ménière-type vertigo with all other possible causes for vertigo excluded or if they have sensorineural hearing loss and disequilibrium with all other causes excluded. According to the AAO-NHS CHE guidelines, Ménière-type vertigo is commonly accompanied by nausea, vomiting, and disequilibrium as well as horizontal nystagmus or horizontal-rotatory nystagmus, which is present during an acute vertigo attack. For

a patient to be diagnosed with “probable” MD, there must be at least one episode of Ménière-type vertigo with all other causes of vertigo excluded in conjunction with audiometric documentation of sensorineural hearing loss on at least one occasion. The patient must also experience tinnitus or aural fullness in the affected ear. For the diagnosis of “definite” MD, patients must have presented all symptoms for the diagnosis of “probable” MD experienced two or more spontaneous episodes of Ménière’s vertigo at least 20 minutes in duration. For the diagnosis of “certain” MD, the person must meet the requirements of “definite” MD, along with confirmation of endolymphatic hydrops through a post-mortem histopathologic examination. Table 4 shows the different AAO-HNS CHE categories and the criteria required for each diagnosis.

**Table 4:** The 1995 AAO-HNS CHE Criteria for the diagnosis of Ménière’s disease (adapted from Members of the Committee on Hearing and Equilibrium, 1995; p. 182).

| Category   | Criteria   |
|------------|--|
| “Possible” | <ul style="list-style-type: none"> <li>- Episodic vertigo of the Ménière type without documented hearing loss, or</li> <li>- Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes</li> <li>- Other causes excluded</li> </ul> |
| “Probable” | <ul style="list-style-type: none"> <li>- One definitive episode of vertigo</li> <li>- Audiometrically documented hearing loss on at least one occasion</li> <li>- Tinnitus or aural fullness in the treated ear</li> <li>- Other causes excluded</li> </ul>                    |

- |            |   |
|------------|---|
| “Definite” | - Two or more definitive spontaneous episodes of vertigo 20 minutes or longer |
|            | - Audiometrically documented hearing loss on at least one occasion            |
|            | - Tinnitus or aural fullness in the treated ear                               |
|            | - Other causes excluded   |
| “Certain”  | - Definite Ménière’s disease, plus histopathologic confirmation               |
- 

The AAO-HNS CHE guidelines were designed to document and diagnose MD in patients and allow appropriate treatment selection and treatment evaluation. With supporting evidence from the MD literature, the AAO-HNS CHE guidelines aim to provide criteria which can consistently and reproducibly assign a diagnosis (Vrabec et al., 2007). The AAO-HNS CHE recommends that only a patient classified as having “definite” or “certain” MD should be reported as having MD. However, it is also recommended that patients with “possible” and “probable” MD constitute important groups of patients to study because investigation in these patients may have the potential to assist in the development of treatments which could prevent patients from deteriorating to “certain” MD. However, these categories are viewed by many researchers as mere groupings of convenience, added respectively to allow for the diagnosis of patients with incomplete clinical symptoms (Stapleton & Mills, 2008). Furthermore, the AAO-HNS CHE criteria are so broad that they may pick up a larger proportion of the patient cohort than would be diagnosed with Prosper Ménière’s full set of diagnostic criteria. It has been noted that although the AAO-HNS CHE guidelines are generally well accepted, the majority of clinicians do not strictly adhere to these criteria and the guidelines are seldom used in research leading to poor comparability between studies (Stapleton & Mills, 2008).

In 2003, Thorp, Shehab, Bance, and Rutka (2003) examined the use of the AAO-HNS CHE criteria in publications about MD. In reviewing 128 MD studies, they found that 79.9% of

papers reported using AAO-HNS CHE criteria in the diagnosis of MD. However, it was revealed that only 50% of those publications used the AAO-HNS CHE criteria correctly to diagnose MD. Examples of failing to comply with the AAO-HNS CHE guidelines included incorrect use of the use of the guidelines where the patient follow-up period was incomplete, use of the guidelines in inappropriate studies or not using the guidelines at all (Thorp et al., 2003). These findings have led to concerns about how these guidelines have been used clinically. Thorp et al. (2003) concluded that increased adherence to the current AAO-HNS CHE criteria among researchers is necessary to make use of findings from MD research.

Stapleton & Mills (2008) analyzed the clinical profiles of 650 patients seen in a balance clinic to compare the AAO-HNS criteria with Menière's original description of MD. Prosper Menière believed that patients with symptoms of intermittent vertiginous episodes lasting for several minutes, along with tinnitus and hearing fluctuations, could be diagnosed as having MD. Menière noted that many patients diagnosed with MD also suffer from a feeling of aural fullness. The AAO-HNS CHE criteria was shown in Stapleton & Mills' (2008) study to be more sensitive and less specific than Menière's corresponding criteria, with three times as many patients being diagnosed with MD using the AAO-HNS CHE criteria (20.8%) than when the original criteria described by Menière was used (6.9%). Based on these findings, the implementation of stricter diagnostic criteria for MD was recommended by the authors.

#### *1.2.3.2 Gibson score*

The Gibson score was established in 1992 by William Gibson to simplify the diagnosis of MD by focusing on the dependence and interaction of vertigo, hearing, tinnitus, and aural pressure, the four most common symptoms experienced by MD patients. The Gibson score differs from other diagnostic tools in that it is based on the complete clinical history of the

patient instead of the symptoms identified at the time of consultation alone (Gibson, 1990). The 10 point score is tabulated based on the presence of the symptoms of vertigo and hearing, which are designated three descriptors each, and the symptoms of tinnitus and aural fullness, which are designated two descriptors each (see Table 5). Each description is worth one point on the 10 point scale and when a description applies to the symptoms of a patient, a point is awarded. After the clinician has finished awarding points where appropriate, the points are added to give a score out of 10. A Gibson score of 7 or higher indicates a diagnosis of MD. The Gibson score provides a helpful summary of patient history and may give clinicians an idea of what the patient’s diagnosis may be. However, like the AAO-HNS CHE guidelines, the Gibson score is a purely subjective assessment. Verbal descriptions from patients are sometimes unclear, inconsistent, and potentially misleading; therefore, medical professionals must exercise prudence when making clinical decisions based on the Gibson score (Gibson, 1990).

**Table 5:** The point system of Gibson score (taken from Kalin, 2010; p.24.)

| Parameter    | Description  | Points |
|--------------|--|--------|
| Vertigo      | - Rotational vertigo   | 1      |
|              | - Attacks of rotational vertigo lasting over 10 minutes  | 1      |
|              | - Rotational vertigo associated/linked with one or more of: hearing loss, tinnitus or aural pressure | 1      |
| Hearing loss | - Sensorineural hearing loss   | 1      |
|              | - Fluctuating sensorineural hearing loss   | 1      |
|              | - Hearing loss or fluctuation associated/linked with one   | 1      |

---

|                |   |    |
|----------------|---|----|
|                | or more of: vertigo, tinnitus or aural pressure   |    |
| Tinnitus       | - Peripheral tinnitus lasting over 5 minutes  | 1  |
|                | - Tinnitus fluctuating or changing with one or more of<br>vertigo, hearing loss or aural pressure | 1  |
| Aural pressure | - Constant aural pressure lasting over 5 minutes  | 1  |
|                | - Aural pressure fluctuating or changing with one or<br>more vertigo, hearing loss or tinnitus    | 1  |
| Maximum score  |   | 10 |

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#### 1.2.4 Physiological Assessments

Since abnormal ECoChG results were first described in ears of patients with MD in 1977, ECoChG has been considered a valuable tool in the diagnosis of MD (Gibson, Moffat, & Ramsden, 1997; Gibson, 2009). Subjective assessments of MD using the AAO-HNS CHE guidelines and the Gibson score, while helpful, should not be used as a substitute for an objective physiological test (Kalin, 2010). It has been proposed that ECoChG should be implemented as a standard clinical assessment for patients with MD symptoms (Saeed, 1998).

##### 1.2.4.1 Electrocochleography (ECoChG)

Electrocochleography provides an electrical picture of inner ear function by measuring the auditory evoked responses (AERs) generated by the cochlea and auditory nerve in response to acoustic stimulation. Click and tone burst stimuli of varying intensities played via headphones evoke an ECoChG waveform, which appears two to three milliseconds after acoustic stimulation (Gibson, 2009).

A normal ECoChG waveform has three components, the cochlear microphonic (CM), summing potential (SP), and compound action potential (AP). The CM signal is an alternating current which replicates the electrical waveform of the acoustic stimulus. The outer hair cells of the cochlea are the main generator of the CM, which is present for the entire duration of the acoustic stimulus. The SP signal is derived from the asymmetric transfer function of the inner hair cells (Ferraro, 2000). The SP is a direct current (DC) potential which appears as shift in the baseline from the CM and follows the stimulus envelope. (Gibson, 2009). The AP, otherwise known as the cochlear compound action potential, is the sum of simultaneously firing cochlear nerve fibres. In ears without MD, the AP has a latency of approximately 1.5 ms and is usually larger than the SP.

Patients with MD usually have an electrocochleogram with greater amplitude for SP relative to AP. Click-evoked ECoChG waveforms are analyzed by calculating the ratio of the summing potential amplitude and action potential amplitude of the response waveform (SP/AP ratio). The amplitudes of SP and AP are usually measured from the peak to the trough of the waveform; however, another technique called the reference demarcation method can also be employed (Ferraro, 2000). Despite the initial promising results shown with this technique, most authors now concede that the poor specificity of click-evoked SP/AP ratio limit its diagnostic ability. The more recent use of tone burst stimuli has enabled the measurement of absolute SP amplitudes and SP/AP at separate frequencies (Gibson, 1996).

There have been some conflicting views on the current clinical value of ECoChG with some authors suggesting that EcoChG testing lacks specificity and sensitivity in the general population. Although most MD literature suggests that ECoChG is highly specific, a number of publications have cited examples where patients with a “definite” 1995 AAO-HNS CHE

diagnosis of MD were shown to be associated with normal electrocochleograms. However, it could be argued that the AAO-HNS CHE criterion has questionable reliability because it is based on subjective measures alone. Some researchers have also questioned the meaningfulness of a negative ECoChG finding, with some evidence showing the relatively low rates of sensitivity in some studies. The large variation of the reported sensitivities is most likely due to methodology differences between studies. A recent study of 178 suspected MD patients by Al-momomani et al. (2009) yielded a sensitivity of 92% and specificity of 82% based on measures of click-evoked amplitude and area ratios and tone burst-evoked SP amplitudes (at 1 and 2 kHz). In contrast, it has been suggested that factors, such as degree of hearing loss, disease duration, and frequency of vertigo attacks, may influence SP/AP ratio amplitude leading to lower sensitivity scores in some studies (Takeda & Kakigi, 2010). Takeda and Kakigi (2010) found that the longer a patient is symptomatic or the more severe the ear symptoms, the stronger the likelihood of an abnormal ECoChG result.

Research on the usefulness of ECoChG for differentiating between MD and vestibular migraine is limited. As part of a wider retrospective study of the medical management of patients diagnosed with vestibular migraine, Johnson (1998) carried out ECoChG recordings in eight patients who were later subjectively diagnosed with vestibular migraine. All of the eight patients experienced relief from their aural fullness and episodic vertigo after receiving medication for vestibular migraine. Positive ECoChG results were previously yielded in five of the eight vestibular migraine patients. This finding caused Shepard (2006) to warn against using ECoChG to discriminate between these two disorders. However, Shepard (2006) suggested that electrophysiological data could be used alongside MRI studies to achieve an objective differential diagnosis.

Auditory evoked responses also form the basis of other electrophysiological assessments, such as the auditory brainstem response (ABR). The application of improved signal averaging in ABR made way for the emergence of ECochG. The ABR is routinely used to test the hearing thresholds of infants and to rule out the presence of retrocochlear pathology in adults. In patients with normally functioning auditory pathways, ABR testing elicits responses from neural and brainstem generators, which are recorded by electrodes attached to the patient's head. Click, tone burst, or chirp stimuli are typically used to elicit the ABR.

A new ABR technique known as CHAMP or cochlear hydrops analysis masking procedure was developed by Don, Kwong, and Tanaka in 2005 to assist with the diagnosis of MD. Its developers demonstrated that they were able to obtain 100% sensitivity and 100% specificity in differentiating between definite MD patients and normal controls. However, a more recent study by De Valck et al.(2007) found that CHAMP was unable to discriminate between MD patients and other non-MD patients with otovestibular symptoms.

#### *1.2.4.2 Endolymphatic Hydrops*

The distension of scala media within the inner ear, otherwise known as endolymphatic hydrops, can be detected with ECochG, confirming the presence of MD. Endolymphatic hydrops is generally accepted to be the primary pathogenic mechanism of MD; however, as previously discussed, the measurement and mechanism of endolymphatic hydrops is controversial and some authors disputed the relationship between MD and endolymphatic hydrops.

Several mechanisms have been proposed to explain how endolymphatic hydrops causes the changes in cochlear and auditory nerve potentials, which can be reflected in abnormal

electrocochleograms. The most accepted theory by Patuzzi (1996, 2009) suggests that the increased volume of endolymph causes mechanical biasing of the organ of Corti.

In a normal cochlea, the inner hair cell (IHC) operating point is near scala tympani (ST) because the hair bundles are velocity coupled. At this position, approximately 10-20% of the mechano-electrical transduction (MET) channels are open at rest in the IHC. The outer hair cell (OHC) operating point is more central as their stereocilia are displacement coupled and consequently, an estimated 40-50% of the OHC MET channels are open at rest. In ears with endolymphatic hydrops, the swelling of scala media causes displacement of the basilar membrane towards ST moving the OHC operating point closer to the IHC operating point. This results in an increase of direct current (DC) component in the OHC receptor current. The SP magnitude increases greatly as there are three times more OHCs than IHCs. The AP also decreases probably because of an OHC motor loss, which decreases the efficiency of the MET to electromechanical transduction (EMT) active process. Other mechanisms involving biochemical and/or vascular changes have also been suggested.

#### *1.2.4.3 Vestibular-evoked myogenic potentials (VEMPs)*

Vestibular-evoked myogenic potentials (VEMPs) are short-latency electric muscle responses, which can be recorded to assess the function of the otolith organs. In addition to sensing linear acceleration, the otoliths of the saccule and utricle have been shown to possess vestigial sensitivity to strong acoustic stimulation (Zhou & Cox, 2004; Brantberg, Löfqvist, Westin, & Tribukait, 2008). Early knowledge of this phenomenon came from Bickford, Jacobson, and Cody (1964), who showed that VEMPs could be recorded in patients with profound hearing loss. Vestibular-evoked myogenic potentials result from a temporary reduction in muscle activity, which is recorded as a positive wave (Hall, 2007). They are measured from

either the sternocleidomastoid (SCM) muscle or the extraocular muscles and can be evoked by a range of acoustic stimuli, including air conduction (AC) clicks, AC tone bursts, and bone conduction (BC) tone bursts as well as mechanical and electrical stimuli such as forehead taps and transmastoid direct current (DC) stimulation (Rosengren, Welgampola, & Colebatch, 2010).

Rauch (2006) found that the MD ears had significantly increased tone burst VEMP thresholds compared with healthy ears. An alteration in frequency-tuning was also noted in affected ears (Adams et al., 2010). Abnormal VEMP findings have also been found in patients with vestibular migraine, suggesting that the site of lesion for this disorder may lie in the sacculocollic pathway (Hong, Kim, Park, & Lee, 2011). A study by Murofushi et al. (2009) found no significant difference between the VEMP responses of vestibular migraine patients and normal controls; however, they did report evidence of the VEMP response tuning to 1 kHz in patients with vestibular migraine as is normally seen in MD VEMP responses (Murofushi et al., 2009).

### **1.2.5 Treatments**

The following section provides information about the different treatments and management options currently used to control the symptoms of MD and migraine, including vestibular migraine.

#### *1.2.5.1 Treatment of MD*

Ménière's disease management focuses on lessening the debilitation caused by MD symptoms, especially vertigo episodes. A range of treatments are commonly used in an attempt to reduce the symptoms of MD; however, current treatments have been shown to be ineffective for some patients. Patients are generally instructed to reduce the amount of sodium in their diet

as well as avoiding caffeine, alcohol, tobacco, chocolate, and stress (Furstenberg, Lashmet, & Lathrop, 1992). However, recently published research found no evidence of higher levels of the stress-triggered heat shock protein 70 (HSP-70) antibody in patients with MD (Hornibrook, et al. 2011). Vestibular suppressants may also be prescribed either to control acute attacks of vertigo or prophylactically, as is the case with betahistine. Conservative methods are often the only option for patients with bilateral MD as alternative ablative treatments come with the risk of bilateral vestibular and cochlear hypofunction (Nabi & Parnes, 2009).

If conservative management proves to be ineffective, a common next step in MD management is a nonablative measure such as the Meniett device, diuretics, or intratympanic steroids. The Meniett device transmits an intermittent pulsatile pressure to the middle ear space which causes changes in inner ear fluid dynamics (Nabi & Parnes, 2009). Several authors have studied the efficacy of the Meniett device. Dornhoffer and King (2008) found, in a long-term study of 21 MD patients, that 75% of these patients reported a decrease in the severity and frequency of vertigo attack following treatment with a Meniett device. However, Boudewyns et al. (2005) failed to show any long-term benefit of Meniett therapy. Some evidence suggests that intratympanic steroids help ease the symptoms of MD. Boleas-Aguirre et al. (2008) reported that 91% of the 129 patients who were intratympanically given the steroid dexamethasone experienced satisfactory control of their vertigo.

If nonablative treatments fail, intratympanic gentamicin therapy is usually trialed in favour of surgical ablation. Pullens and van Bentham (2011) reviewed two gentamicin trials involving 50 participants and concluded that the use of intratympanic gentamicin was effective in the treatment of vertigo. The use of surgical interventions, such as vestibular neurectomies,

labyrinthectomies, and endolymphatic sac surgeries, has declined since the 1990s and is usually attempted only as a last option (Ruckenstein, 2010; Silverstein et al., 2003).

#### 1.2.5.2 *Treatment of Migraine and Vestibular Migraine*

As little is known about the pathophysiology of vestibular migraine, the majority of patients diagnosed with this condition are managed according to migraine treatment guidelines. Management of vestibular symptoms typically begins with removing known “migraine-triggering” foods such as aged cheese, processed meats, red wines, caffeine, and foods containing monosodium glutamate (MSG) from the patient’s diet, along with lifestyle modifications such as regular exercise, a balanced diet, and good sleeping habits (Fotuhi et al., 2009; Mikulec, Faraji, & Kinsella, 2012). In addition, vestibular physical therapy may benefit selected vestibular migraine patients. A study by Whitney et al. (2000) found that patients with vestibular migraine demonstrate improved physical performance and a greater self perception of their abilities after vestibular physical therapy.

A large number of prophylactic migraine pharmaceuticals have been used to control the symptoms of vestibular migraine including, but not limited to, tricyclic antidepressants (TCAs), beta-blockers, calcium channel blockers and anti-seizure medications (Reploeg & Goebel, 2002; Mikulec, et al., 2011). A study by Mikulec et al. (2011) reported that the TCA nortriptyline, as an initial or secondary treatment, was an effective treatment in 47% of vestibular migraine patients, significantly more effective at improving symptoms compared with diet management alone. Another study which monitored patients whose treatment plan included initial dietary manipulation followed, if necessary, by either TCAs, beta-blockers, calcium channel blockers or anti-seizure medications found that 72% of the patients experienced a greater than 75% reduction in the frequency of vestibular migraine symptoms (Reploeg & Goebel, 2002).

A class of drugs called benzodiazepines, which are commonly used to suppress the vestibular system, have been used to prevent vestibular migraine episodes; however, these drugs can cause addiction problems and for this reason some physicians may only prescribe these drugs after other medications have failed. For acute relief from the symptoms of vestibular migraine, abortive migraine drugs such as Sumatriptan and Zolmitriptan may be prescribed. In practise, pharmacologic treatment of vestibular migraine frequency involves a trial and error process of prescribing various medications (Mikulec et al., 2011). As the treatment options of described in this section differ depending on whether patients are diagnosed with MD and vestibular migraine, it is extremely important that the differentiation of these two disorders is correct. As the current AAO-HNS CHE guidelines for the diagnosis of MD do not include objective assessments, some patients with vestibular migraine may be misdiagnosed as having MD and subsequently receive inappropriate treatment.

### **1.3 Research Question**

The purpose of this study is to investigate whether ECochG measures assist in differentiating between suspected MD patients with and without a past history of migraine. Many authors have noted an association between MD and migraine, yet this remains a controversial area which would benefit from more research. In addition, due to the conflicting demographic data which has been reported in recent epidemiological studies, further investigation of MD is justified by the need to clarify the demographics of MD patients.

## 1.4 Aims and Hypotheses

The main purpose of this study was to determine whether ECoChG measures were sensitive in differentiating between patients with and without migraine. The two major research questions of the study were:

- 1) **Electrocochleography as a tool for differential diagnosis:** Can ECoChG measures assist in differentiating between suspected MD patients with and without a past history of migraine?
- 2) **Demographic characteristics of MD:** Are the demographic findings from this study in agreement with previous studies?

To answer these questions, a comparison was conducted between three neural symptom groups, all of which had experienced vertigo, including patients with a history of migraine (“Migraine”), patients with no history of migraine but with reported headache (“No migraine-with headache”), and patients with neither history of migraine nor reported headaches (“No migraine-without headache”). Based on the literature which suggests that the vertigo variant of migraine (vestibular migraine) may be caused by a central disturbance such as cortical spreading of depression while MD is caused by endolymphatic hydrops, it was hypothesized that these three groups would show a difference in the ECoChG results as well as in the symptomatic and demographic characteristics. Specifically, three hypotheses were listed as follows:

- (1) There will be a greater proportion of “negative” ECoChG cases in the “Migraine” group compared to the two “No migraine” groups (i.e., “No migraine-with headache” and “No migraine-without headache” groups).

- (2) Patients with a history of migraine would have characteristics different from those of patients without a history of migraine.
- (3) The demographic characteristics of the patients with confirmed MD would fit within the range of demographic data published in previous papers.

The rationale for the first hypothesis is related to the current theories on the aetiology of vestibular migraine as previously described. As MD and vestibular migraine are caused by different pathologies, it is most likely that a “positive” ECochG result, which is considered a strong indicator of the pathology associated with MD, would occur less frequently in the “migraine” group. Likewise, the rationale for the second hypothesis is that a history of migraine is a sign of vestibular migraine which has different symptoms compared to MD. The rationale for the third hypothesis is that current published demographic data is wide-ranging and highly variable and thus data from this study is likely to fall within the range reported in previous research.



## Chapter Two: Methodology

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### 2.1. Participants and Participants' Task

Based on a quota sampling method, a total of 395 patients referred to and assessed at the department of Otolaryngology of Christchurch Hospital (Christchurch, New Zealand) between 1993 and 2011 for suspected MD were included as participants. The clinical information, hearing test results, and ECoChG data recorded for these participants were retrieved from the hospital database. Ethical approval was obtained from the University of Canterbury Ethics Committee and the Upper South A Regional Ethics Committee from the New Zealand Ministry of Health, Health and Disability Ethics Committee. All the participants included in this study had verbally consented to having their otolaryngology and audiology files being used for research. The inclusion criteria for the participants were: having undergone a comprehensive clinical examination, ECoChG assessment, and a puretone audiogram testing on the day of the ECoChG assessment and had the corresponding records of the attending physician's reporting of the participant's AAO-HNS CHE classification (possible, probable, definite, and certain) and Gibson (1-10) score. Information on the participant's age at the onset of their vertigo, age of onset of their first MD symptom (vertigo, hearing loss, tinnitus or aural pressure), and ethnicity were also required. Patients were excluded from the main study group if they did not have a history of disequilibrium and thus had a Gibson score of 0 for vertigo. Consequently, a total of 24 patients were excluded from the study because they did not have vertigo. This "no vertigo" group consisted of 16 males and 8 females, aged between 15 and 86 years (Mean = 56 years, SD

= 19). Observations made for this no vertigo group are shown in Appendix 1. Patients with both a “positive” ECochG finding and a diagnosis of “definite MD” under the AAO-HNS CHE guidelines were classified as having “clinically certain MD”.

The patients selected for this study consisted of 187 males and 184 females, aged between 16 and 93 years, with a mean of 59.4 years (SD = 14.2). All of these participants had reportedly experienced vertigo. Among these patients, 5 males and 24 females, aged between 35 and 90, with a mean of 60.7 years (SD = 14.6), were diagnosed with migraine by an otolaryngologist with guidance from the 2004 ICHD criteria (“Migraine group”). Specifically, patients previously diagnosed with migraine by a neurologist, along with patients who had not previously received a migraine diagnosis but had a history of headaches accompanied by photophobia and phonophobia or vomiting/nausea, were included in the “Migraine” group. The second group included 7 males and 16 females, aged between 50 and 80, with a mean of 59.3 years (SD = 14.2), who were shown on the records to have no specific migraine features recognized but have experienced headaches with vertigo attacks (“No migraine-with headaches”). The third group included 175 males and 144 females, aged between 16 and 93, with a mean of 59.1 years (SD = 14.4), who showed no indication of migraine or headache (“No migraine-without headaches”).

An audiologist assessed the hearing of each patient prior to consultation with an otolaryngologist. The pure tone audiogram of each patient was ascertained using the modified Hughson-Westlake “ascending” method of threshold detection (Carhart & Jerger, 1959). Air conduction thresholds were tested at 250, 500, 1000, 2000, 4000 and 8000 Hz bilaterally while bone conduction thresholds were tested in participants found to have air conduction thresholds

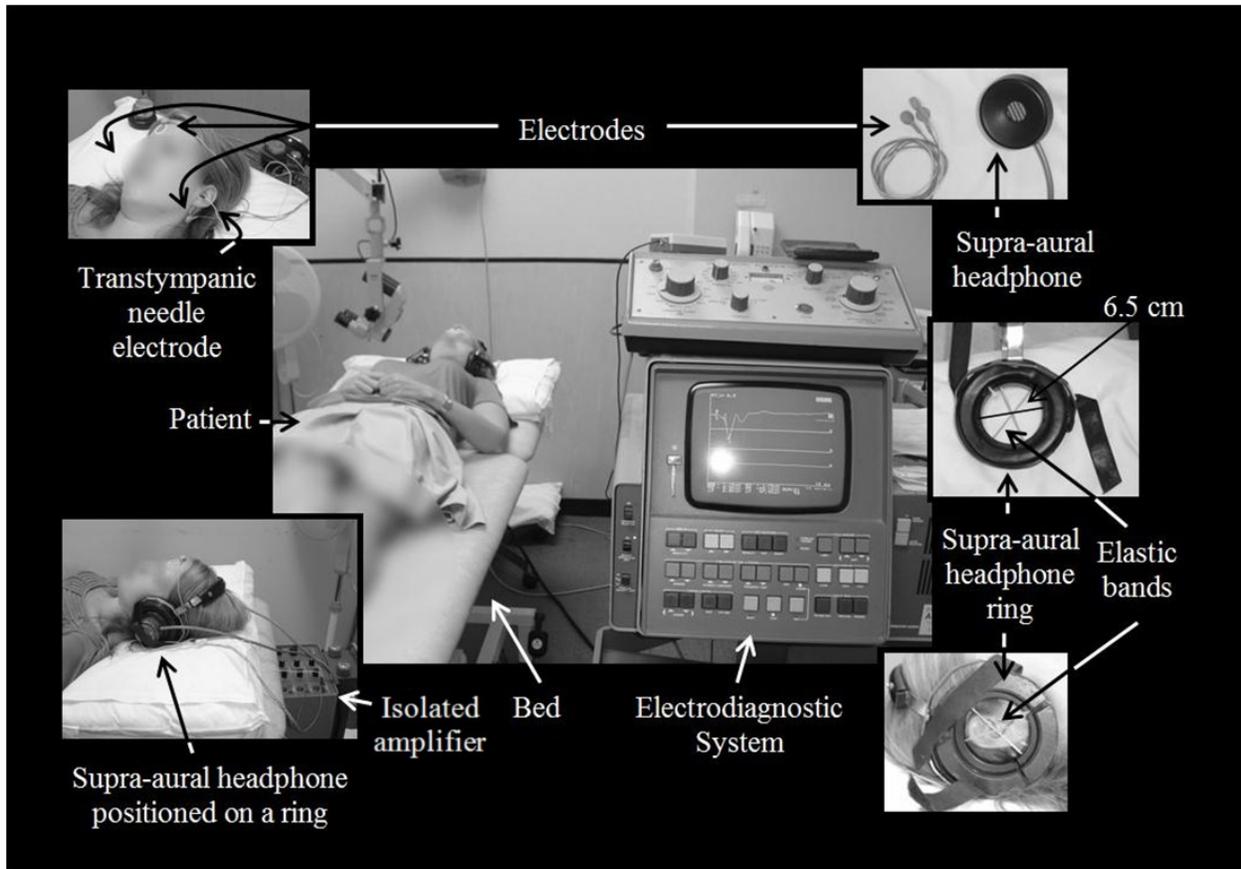
greater than 20 dB HL at 500, 1000, 2000, and 4000 Hz. Bone conduction thresholds enabled the audiologist to differentiate between conductive and sensorineural hearing loss.

The otolaryngologist recorded a thorough case history and performed vestibular and auditory assessments. The vestibular examination consisted of the Romberg test, Unterberger Stepping Test, and Head-thrust test, whereas the auditory assessments included otoscopy and tuning fork tests (Weber and Rinne). Examinations of the patient's eye movements were also performed to indicate the presence or absence of nystagmus as well as additional tests to examine cranial nerve function and cerebellum function. Patients with symptoms and test results suggestive of MD were referred for ECoChG testing by the otolaryngologist and placed on the ECoChG waiting list. As needed medications such as Betahistine were prescribed by the otolaryngologist to help patients with MD symptoms, the otolaryngologist also instructed patients to moderate their intake of salt. Any previous medical interventions chosen for patients were reassessed after ECoChG testing. The patients were reviewed on an annual basis unless patients reported any difficulties with their symptoms or medication.

## **2.2. Instrumentation**

The Amplaid MK 15 (Amplaid SPA Milan, Italy), a multichannel diagnostic system was used to record the ECoChG signals of the participants. The Amplaid MK 15 system is calibrated by ECS Ltd, New Zealand on an annual basis. The other components of the testing equipment, as illustrated in Figure 1, included a sterile insulated transtympanic needle electrode, phenol, elastic bands, a supra-aural headphone, and disposable electrodes (Ambu Blue Sensor electrodes, Denmark). Three disposable electrodes were attached to the patients, with the ground electrode being placed on the patient's forehead (Fz) and an indifferent electrode being attached to the left

and right mastoid process respectively. The fourth electrode (transtympanic needle) was passed through the tympanic membrane to rest on the promontory in the round window niche. The four electrodes were wired to a biological amplifier, which in turn was connected to the Amplaid diagnostic system through long cable. Long cables also connected the supra-aural headphone with the diagnostic system.



**Figure 1:** Instrumentation setup (adapted from Kalin, 2010).

### 2.3. Procedure

The patients attended the department of Otolaryngology at Christchurch Hospital for ECoG testing. The procedure of the ECoG test was explained to the patient. The skin on their forehead and behind their ears was prepared through gentle abrasion with fine medical

sandpaper. A small amount of conduction paste was applied to three disposable electrodes, which were then placed on the forehead and behind the ears on the mastoid process. The patient was instructed to lie face up on the bed while the otolaryngologist performed otoscopy and removed any cerumen from the external auditory meatus. The otolaryngologist anaesthetised the tympanic membrane by applying a drop of phenol on the surface of the membrane. After the insertion of the active needle electrode in the test ear, the position of the needle electrode was maintained by two elastic bands stretched across a 6.5 cm diameter ring resting on the auricle. The acoustic stimulus was then coupled to the ear of the patient by sitting the supra-aural headphones on the 6.5 cm ring. The patient was instructed to stay lying on the bed to minimise muscle noise in the ECoChG recording. Tone burst and click stimuli were employed to elicit the ECoChG auditory evoked response (AER). The recording parameters used for the click stimulus were: a 100  $\mu$ s click duration, 95 dBnHL click intensity, alternating polarity at a rate of 10 times per second, a total of 256 click presentations used per run, and an analysis time window of 10 ms for AER signals. Tone burst were presented at an intensity of 100 dBnHL at the frequencies of 500, 1000, 2000, and 4000 Hz. The tone burst had a rise time of 1 ms, a 14 ms plateau, and 1 ms fall time. Other parameters for the tone burst stimulus included a total of 1,024 presentations used per run and an analysis time window of 30 ms for AER signals. A band-pass filter was used to filter both the AER response and the click and tone burst stimuli retrospectively. The filter was assembled from a high-pass filter with the cut-off frequency at 0.5 Hz and a 6 dB per octave filter slope and a low-pass filter at 3 kHz with a 12 dB per octave filter slope.

## **2.4. Measurement**

The experimental measures were obtained from pure tone audiometry and three types of diagnostic assessments: Gibson score, AAO-HNS CHE, and ECoChG test results. A description of these measures and the method used to derive them are as follows.

### **2.4.1. Pure Tone Audiometry Measurements**

Pure tone audiogram data recorded on the day of the patient's ECoChG assessment was retrieved from the otolaryngology and audiology files. An audiologist recorded the patient's air conduction thresholds at five frequencies: 500, 1000, 2000, 4000, and 8000 Hz.

### **2.4.2. Gibson Score Measurements**

The otolaryngologist used the standard point system as shown in Table 5 to calculate a Gibson score for patients immediately before ECoChG assessment. Each patient may have more than one documented Gibson score as the otolaryngologist may also calculate a Gibson score at the initial consultation or at follow-up appointments.

### **2.4.3. AAO-HNS CHE Measurements**

The otolaryngologist used the guidelines of the AAO-HNS CHE criteria to classify each patient with "possible", "probable", "definite", or "certain" MD. The AAO-HNS CHE criterion is shown in Table 4. The otolaryngologist also recorded additional details on interesting any patient symptoms or clinical history including: descriptions of hearing loss, vertigo attacks, tinnitus, and aural fullness as well as head trauma, other auditory or vestibular conditions, history of MD in family, migraine or headache history.

#### **2.4.4. Electrocochleography Measurements**

ECochG recordings were obtained bilaterally in response to auditory stimulation from the tone burst and click stimuli. The magnitude of the summing potential (measured in  $\mu\text{V}$ ) and action potential (measured in  $\mu\text{V}$ ) evoked from tone bursts and clicks were compared to their respective normative values shown in Table 6. Summing potential / action potential ratios (in %) were also calculated for the tone burst and click evoked responses and then compared to the normative values. Tone bursts were presented at the four following frequencies, 500, 1000, 2000 and 4000 Hz giving reliable frequency specific information.

### **2.5. Data Analysis**

The participant's name, age, gender, race, national health index number, and presence of migraine or headache history were entered into the database. In addition to this demographic data, test results from puretone audiometry and ECochG assessments, as well as information pertaining to the Gibson score and AAO-HNS CHE criteria, were also tabulated. Patient audiometric thresholds, the Gibson score, SP and AP magnitudes were entered directly from the patient files into the database. The classification of patients under the AAO-HNS CHE criteria, however, required detailed examination of the patient's otolaryngology and audiology records, in particular the specific information about the MD symptoms they had experienced. The patient notes were compared against the AAO-HNS CHE criteria in order to assign a diagnosis (See Table 4).

The diagnosis of "positive" ECochG was based on the voltage classification scheme, as shown below in Table 6.

**Table 6:** ECoChG norms (adapted from Kalin, 2010 (originally adapted from Gibson, 1994)).

Clicks: Abnormal if SP/AP ratio  $\geq 0.50$

Tone Bursts:

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| Tone Burst Frequency | Hearing Level dBHL | Abnormal if SP $\leq$ |
|----------------------|--------------------|-----------------------|
| 500 Hz (75 DBHL)     | under 25           | -2 $\mu$ V            |
|                      | 20 - 35            | -2 $\mu$ V            |
|                      | 40 - 55            | -2 $\mu$ V            |
|                      | 60 - 75            | -1 $\mu$ V            |
| 1 kHz (90 DBHL)      | under 25           | -6 $\mu$ V            |
|                      | 20 - 35            | -6 $\mu$ V            |
|                      | 40 - 55            | -6 $\mu$ V            |
|                      | 60 - 75            | -3 $\mu$ V            |
| 2 kHz (100 DBHL)     | under 25           | -9 $\mu$ V            |
|                      | 20 - 35            | -7 $\mu$ V            |
|                      | 40 - 55            | -5 $\mu$ V            |
|                      | 60 - 75            | -5 $\mu$ V            |
| 4 kHz (75 DBHL)      | under 25           | -9 $\mu$ V            |
|                      | 20 - 35            | -5 $\mu$ V            |
|                      | 40 - 55            | -5 $\mu$ V            |
|                      | 60 - 75            | -5 $\mu$ V            |

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## **2.6. Statistical Analysis**

Patients were classified as “ECochG positive” if they had any SP values from either click or tone burst stimuli which were greater than the normative data values, as specified in Table 6. Patients were classified as “ECochG negative” if none of their SP recordings were greater than the normative data values. A series of chi-square tests were conducted to compare the distributions of gender and ECochG classifications in the comparison groups. For the gender distributions of patients with “clinically certain” MD, as well as the ECochG results for patients with or without migraine, the odds ratios are calculated (for definition of odds ratio, see Glossary). For ECochG measures obtained from different frequencies, the coefficient of variation (COV) was calculated (for definition of COV, see Glossary). A series of t-tests were conducted to compare the three patient groups on the hearing thresholds and the COV of the SP/AP ratios. The significance level was set at 0.05. The statistical analysis was performed using the SPSS (version 19) software.



## Chapter Three: Results

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This chapter presents findings from comparisons of ECoChG measures, subjective test results (i.e., AAO-HNS measures and Gibson score), hearing test results, and demographic information between the “Migraine”, “No migraine-with headache”, and “No migraine-without headache” groups.

### 3.1. ECoChG Measures

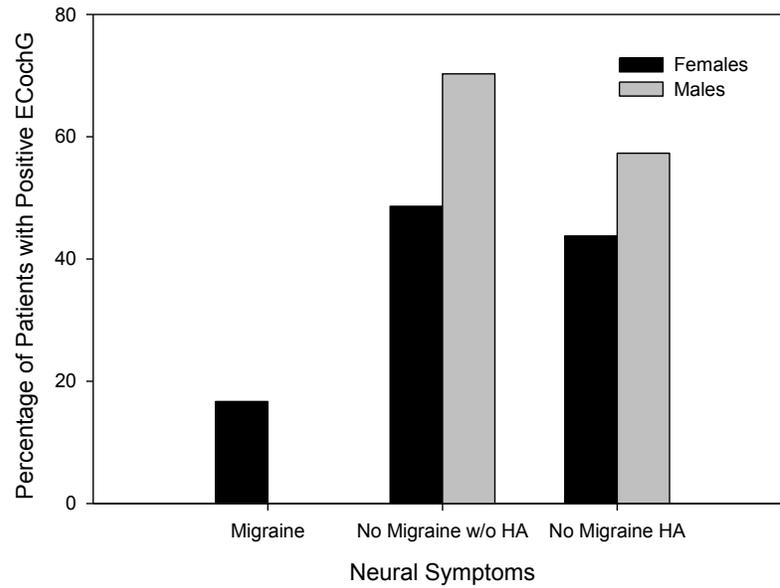
This section describes the distribution of “positive” ECoChG cases across the three comparison groups, the relationship between ECoChG measures at different frequencies, and the progression of hearing loss in individuals identified as “ECoChG positive”.

#### 3.1.1. ECoChG Results in the Presence of Neural Symptoms

Figure 2 shows the percentage of patients identified as “ECoChG positive”, for both males and females, for the “Migraine”, “No migraine-with headache”, and “No migraine-without headache” groups respectively. As shown in Figure 2, there was a lower proportion of “positive” ECoChG cases in the “Migraine” group (13.79%), with both genders combined, than the other two groups, namely, the “No migraine-without headache” (60.50%) and “No migraine-with headache” group (47.83%). Of the patients with “negative” ECoChG results 25 out of 163 (15.34%) were in the migraine group, compared with 4 out of 208 (1.923%) in the patients with “positive” ECoChG results. Results of nonparametric tests revealed that there were significantly more “negative” than “positive” ECoChG cases in the “Migraine” group (chi-square = 15.207,  $df = 1$ ,  $p < 0.001$ ) but more “ECoChG positive” than “ECoChG negative” identifications in the “No

migraine-without headache” group (chi-square = 14.072, df = 1, p < 0.001). There was no significant difference between the number of “ECochG positive” and “ECochG negative” identifications in the “No migraine-with headache” (chi-square = 0.043, df = 1, p = 0.835). The prevalence of “ECochG negative” identifications was significantly higher in the “Migraine” group than both the “No migraine-with headache” (chi-square = 5.675, df = 1, p = 0.017) and “No migraine-without headache” groups (chi-square = 21.748, df = 1, p < 0.001), which were not significantly different from each other (chi-square = 0.954, df = 1, p = 0.329). The odds ratio calculated for the “Migraine” group also suggests that individuals identified as “ECochG negative” 9.2 times more likely to be present in the “Migraine” group than those identified as “ECochG positive”.

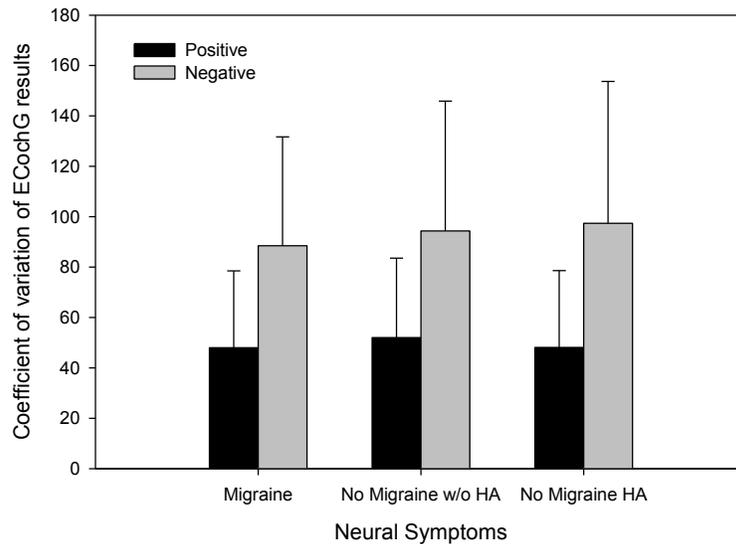
There was a significant difference in the gender distribution of the “Migraine” group (chi-square = 12.448, df = 1, p < 0.001). In the “Migraine” group, which consisted of 24 females and 5 males, all the patients identified as “ECochG positive” were females. There was no significant difference in the gender distribution in the “No migraine-without headache” (chi-square = 3.013, df = 1, p = 0.083) and “No migraine-with headache” groups (chi-square = 3.422, df = 1, p = 0.061). However, among all the patients identified as “ECochG positive”, there was significantly more males than females in the “No migraine-without headache” group (chi-square = 14.554, df = 1, p < 0.001) but no significant gender difference in the “No migraine-with headache” group (chi-square = 0.818, df = 1, p = 0.366). In the "Migraine group" no males were identified as "ECochG positive".



**Figure 2:** The percentage of patients identified as "ECoG positive" for the male and female participants in the "Migraine", "No migraine-with headache", and "No migraine-without headache" groups respectively.

### 3.1.2. Relationship between ECoChG Results at Different Frequencies

Figure 3 shows the COV of the SP/AP ratios as measured at four frequencies (0.5, 1, 2, and 4 kHz) for the “positive” and “negative” ECoChG cases in the three comparison groups (i.e., “Migraine”, “No migraine-with headache”, and “No migraine-without headache”) respectively. Data from both ears of each patient was selected for statistical analysis. It was found, in these three neural symptom groups, that patients identified as “ECoChG positive” had a significantly lower average COV than patients identified as “ECoChG negative” in all of the “Migraine” ( $t = 194.0$ ,  $p = 0.005$ ), “No migraine-with headache” ( $t = 169.0$ ,  $p = 0.014$ ), and “No migraine-without headache” groups ( $t = 29533.0$ ,  $p < 0.001$ ).



**Figure 3:** The coefficient of variation of SP/AP ratios obtained at 0.5, 1, 2, and 4 kHz participants with a history of migraine (“Migraine”), with no history of migraine but with reported headache (“No migraine-with headache”), and without either migraine

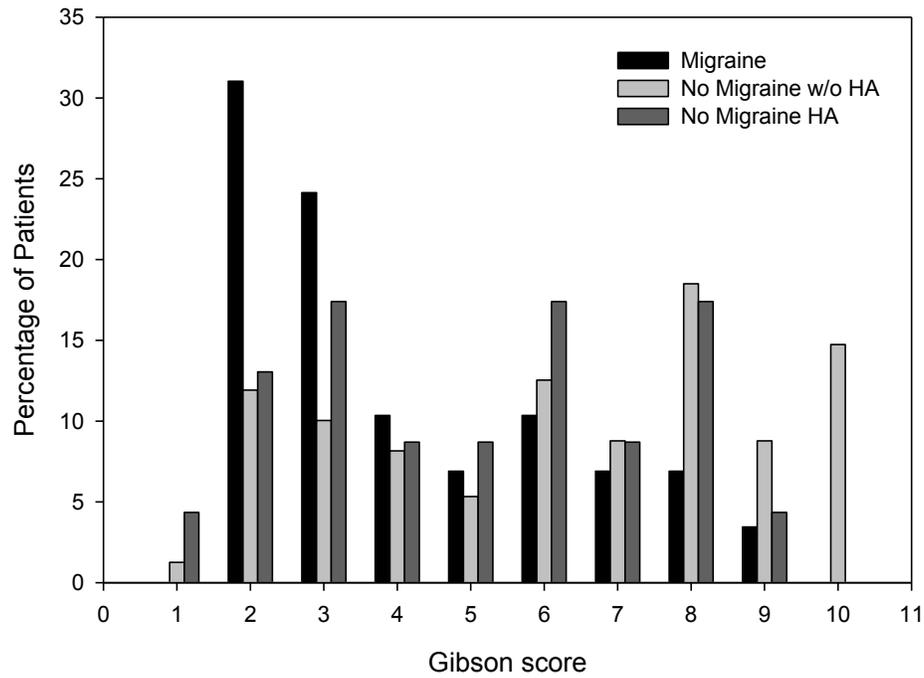
or reported headaches with attacks of vertigo (“No migraine-without headache”) respectively.

### **3.2. Gibson Scores and Hearing Test Results**

Results on the characteristics of patients with different neural symptoms are reported in this section, including Gibson scores and hearing test results.

#### **3.2.1. Gibson Score in the Presence of Neural Symptoms**

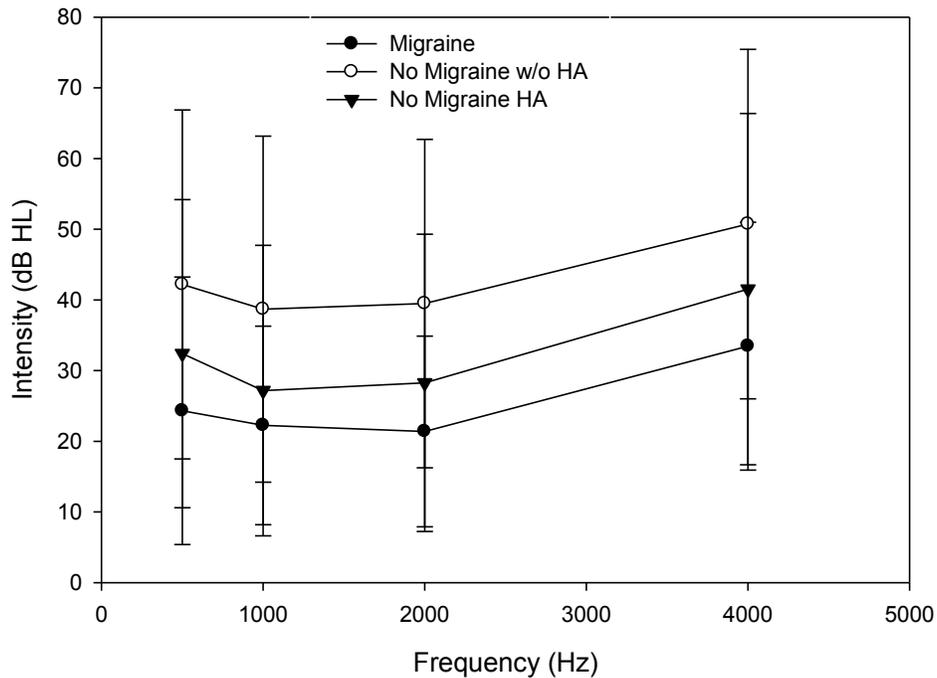
Figure 4 shows the percentage of “migraine”, “No migraine-without headache”, and “No migraine-with headache” patients across ten levels of the Gibson scale. A greater percentage of patients were found to have a lower Gibson score in the “Migraine” group than in the “No migraine-without headache” and “No migraine-with headache” groups, whose scores are more evenly distributed along the scale. A significant difference in the distribution of the Gibson scores was found in the “No migraine-without headache” group (chi-square = 67.415, df = 9,  $p < 0.001$ ), with the score 8 being mode and the distribution being skewed to the left. The distribution of Gibson scores across the Gibson scale was not significantly different in the “Migraine” (chi-square = 13.759, df = 7,  $p < 0.056$ ) or the “No-migraine-with-headache” group (chi-square = 4.783, df = 8,  $p = 0.781$ ). The distribution of the Gibson scores in the “No migraine-without headache” group and the “Migraine” group were found to be significantly different (chi-square = 18.210, df = 9,  $p = 0.033$ ) while no significant difference in the distribution of the Gibson scores was found between “No migraine-without headache” and “No migraine-with headache” groups (chi-square = 6.371, df = 9,  $p = 0.702$ ).



**Figure 4:** The percentage of participants who had a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”) across ten levels of the Gibson scale.

### **3.2.2. Hearing Test Results for Three Neural Symptom Groups**

Figure 5 shows the average thresholds (0.5, 1, 2, and 4 kHz of the worst hearing ear) of patients divided into three groups based on their neural symptoms (“Migraine”, “No migraine-with headache”, “No migraine-without headache”). It was observed that the lowest average audiometric thresholds across all frequencies were found in the “Migraine” group, followed in order by the “No migraine-with headache” and “No migraine-without headache” groups. The threshold intensities of the “Migraine” and “No migraine-without headache” groups were significantly different for all the four frequencies tested 500 Hz ( $t = 3080$ ,  $p < 0.001$ ), 1000 Hz ( $t = 3340$ ,  $p < 0.001$ ), 2000 Hz ( $t = 2948$ ,  $p = 0.001$ ), and 4000 Hz ( $t = 3100.5$ ,  $p < 0.001$ ). Significant differences in threshold intensity were also found between “No migraine-without headache” and “No migraine-with headache” groups at 1000 Hz ( $t = 2971.5$ ,  $p = 0.033$ ) and 2000 Hz ( $t = 2941$ ,  $p = 0.028$ ).



**Figure 5:** Puretone thresholds intensities (dB HL) across frequencies from 500 Hz to 4000 Hz in patients with a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”).

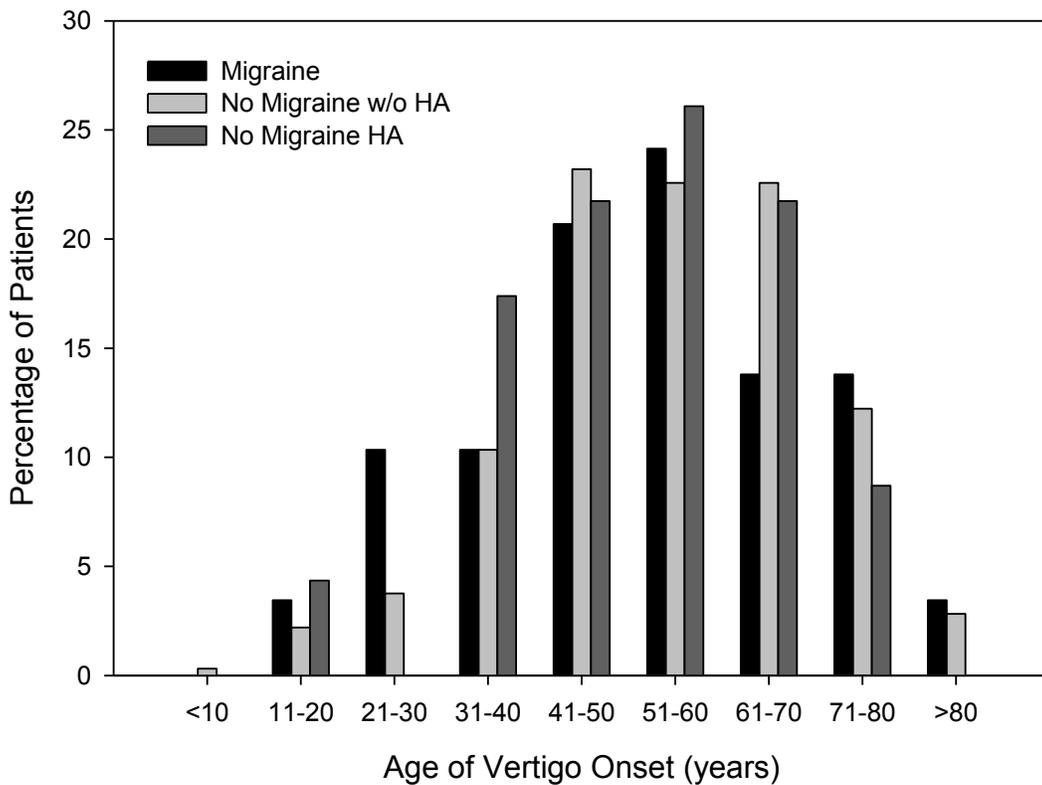
### 3.3. Demographic Information

Demographic information for patients with different neural symptoms and patients with “clinically certain MD” are reported in this section.

#### 3.3.1. Age of Vertigo Onset in the Presence of Neural Symptoms

The distributions of age of vertigo onset in the three neural symptom (“Migraine”, “No migraine-with headache”, “No migraine-without headache”) groups are shown in Figure 6. On

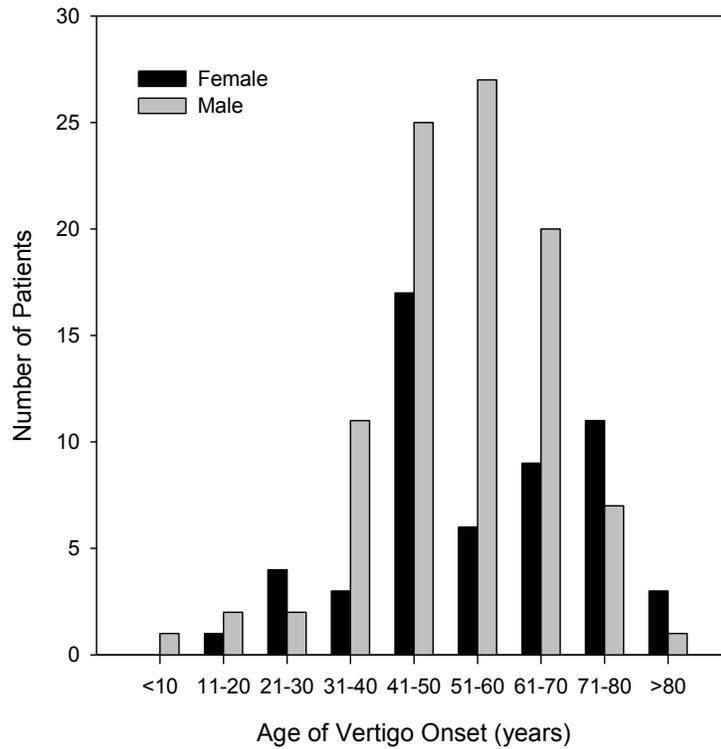
average, patients in the “Migraine” group had the earliest onset of vertigo (51.31 years), followed in order by the “No migraine-with headache” (52.13 years) and “No migraine-without headache” (54.45 years) groups. The distribution of vertigo onset where comparable for all the three groups, with the majority of patients first experiencing vertigo in the 41-50, 51-60, and 61-70 age groups.



**Figure 6:** The distribution of age of vertigo onset in participants who had a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”).

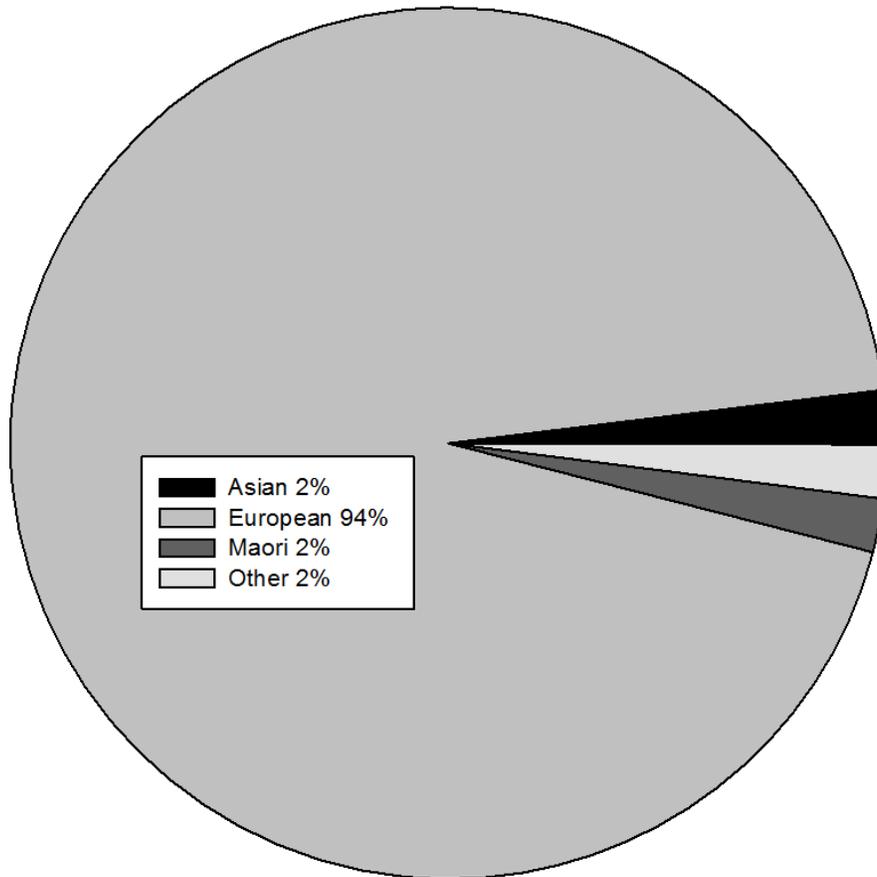
### **3.3.2. Demographic Characteristics of “Clinically Certain Ménière's Disease”**

In patients with classified as having “clinically certain MD”, the average age of vertigo onset was 54.06 years with both male and female data combined. The median age of vertigo onset was also found to be 54 with the patient’s ages ranging from 9 to 90 years. The distributions of age of vertigo onset in male and female participants are shown in Figure 7. The majority of male patients were from the 41-50, 51-60, and 61-70 age groups while the ages of the female patients were comparatively evenly distributed over all age ranges. Results from non-parametric tests revealed that the differences in the age distribution of male and female patients were not significant (chi-square = 12.861, df = 8, p = 0.117). The odds ratio for this data suggests that males are 2.5 times more likely to be identified as having “clinically certain MD” than females. Males were over-represented in the clinically significant MD group as only 30% (55 out of 184) of female participants were diagnosed as having “clinically significant MD” compared to 51% (96 out of 187) of male participants.



**Figure 7:** The distribution of age of vertigo onset in female and male with participants clinically certain MD.

The ethnicities of patients with “clinically certain” MD in this study are shown in Figure 8. The majority of the patients were of European ethnicity, followed by small number of Maori, Asian and other ethnicities.



**Figure 8:** Ethnicity of patient with clinically certain MD.

### 3.4. Summary of Main Findings

Patients in the “Migraine” group were found to have a high proportion of “negative” ECoHG findings while patients in the “No migraine-with headache” and “No migraine-without headache” groups were found to have significantly more “positive” ECoHG results. The coefficient of variation of SP/AP values across all three patient groups was significantly greater in patients with “negative” ECoHG results.

A large proportion of “migraine” patients had a lower Gibson score compared with the patient in the “No migraine-with headache” and “No migraine-without headache” groups, whose

scores are more evenly distributed along the scale. It was observed that patients with “Migraine” generally had lower audiometric thresholds compared with patients with “No migraine-with headache” and patients with “No migraine-without headache” exhibited the highest audiometric thresholds.

The average age of vertigo onset in patients with “clinically significant MD” was 50 - 60 years. A larger than expected numbers of males were diagnosed as having “clinically significant MD”; however, the distribution of ages was not significantly different for males and females. The majority of patients with “clinically significant MD” were of Caucasian ethnicity.



## Chapter Four: Discussion

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The main focus of this study was to determine whether ECoChG measures are sensitive in differentiating between patients with and without migraine. Findings from this study suggest that the “Migraine” group had more “negative” than “positive” ECoChG cases compared to the two groups of patients without migraine (i.e., “No migraine-with headache” and “No migraine-without headache”). Comparison of the symptoms and characteristics of the patients in the three comparison groups also revealed some significant differences in the Gibson score and puretone hearing thresholds. These findings provide evidence suggesting that some patients with suspected MD, particularly those with a history of migraine and “negative” ECoChG results, may have a vestibular variant of migraine called vestibular migraine rather than MD.

### **4.1. Electrocochleography as a Tool for Differential Diagnosis**

The first hypothesis posed in this study was that a greater proportion of “negative” ECoChG cases would be present in the “Migraine” group compared to the two “No migraine” groups (i.e., “No migraine-with headache” and “No migraine-without headache” groups). The finding that patients in the “Migraine” group had a significantly higher proportion of “negative” ECoChG results than the “No migraine-without headache” group and “No migraine-with headache” group supports this hypothesis. This finding suggests that ECoChG assessment may be useful for differentiating between patients with migraine and those with MD. The gender distribution of ECoChG results was unbalanced in the “Migraine” group with all of the male patients having “Negative” findings. Currently, most otolaryngologists use the AAO-HNS CHE criterion in isolation to diagnose MD. The AAO-HNS CHE criterion provides a subjective

method of diagnosing MD. As this subjective approach relies on both patients accurately reporting their symptoms and on the interpretation of the otolaryngologist, the criterion is vulnerable to inaccuracy. In addition, the differentiation between MD and vestibular migraine without using an objective measure can be challenging. The present finding provides preliminary evidence in support of the use of ECoChG assessment to assist in the differential diagnosis for patients suspected of having MD.

Vestibular migraine is a condition of uncertain aetiology where patients experience vertigo and migraine attacks and less commonly, hearing loss and tinnitus (Johnson, 1998). Estimations suggest that between 10% and 15% of adults experience tinnitus and many people develop some degree of hearing loss as they age, albeit frequently at high frequencies rather than showing the characteristic rising or peak audiograms of MD (Huppert et al., 2010). Due to the relatively high prevalence of tinnitus (10-15%) and vertigo (10% in females and 4% in males) in the general population, as well as high rates of hearing loss (45%) in patients over the age of 48 years, a significant proportion of patients with vestibular migraine present with symptoms characteristic of MD (Cruikshanks, et al. 1998; Johnson, 1998; Baloh, 2006; Henry, Dennis, & Schechter, 2005). Therefore, objective tools, such as ECoChG, VEMPs, and MRI are required to differentiate between vestibular migraine and MD. The results from this study show that there were significantly more “negative” than “positive” ECoChG cases in the “Migraine” group compared to the “No Migraine” groups. This finding suggests that the presence of headaches does not indicate the presence or absence of either disorder. Since a proportion of patients with “negative” ECoChG results showed a history of migraine attacks, it appears that at least in these individuals, the vertigo was related to the migraine instead of MD.

The mean COV values of the SP/AP ratios from ECoChG at 0.5, 1, 2, and 4 kHz were found to be lower in ears with “positive” ECoChG results compared to ears with “negative” ECoChG results. These results suggest that SP/AP ratios with low variation across the four frequencies may be an indicator of MD (Kalin, 2010). One explanation for the low variation of the SP/AP ratios in “positive” ears is that the endolymphatic hydrops causes an enlarged SP at all the frequencies and thus the readings at different frequencies become more uniform. This explanation supports the use of ECoChG in the detection of endolymphatic hydrops and MD.

The second hypothesis posed in this study was that patients with a history of migraine would have characteristics which differ from patients without a history of migraine. Comparisons of the symptoms and puretone hearing thresholds of the patients in the “Migraine”, “No migraine-with headache”, and “No migraine-without headache” groups support this hypothesis, suggesting that more than one disorder is present in the study population. A greater percentage of patients in the “Migraine” group had a lower Gibson score compared with patients in the “No migraine-without headache” and “No migraine-with headache” groups, whose scores are more evenly distributed along the scale. The four symptoms of vertigo, hearing loss, aural fullness, and tinnitus make up the Gibson score criteria (Members of the Committee on Hearing and Equilibrium, 1995). Vertigo was present in all participants included in this study, therefore the differences in Gibson score between “Migraine” group and the “No migraine-without headache” and “No migraine-with headache” groups is due to patients experiencing lower rates and lesser degrees of hearing loss, aural fullness, and tinnitus. Further investigation into the hearing thresholds of the three groups of patients has supported this, showing that patients in the “Migraine” group had significantly lower puretone audiometry thresholds than the patients in the “No migraine-without headache” and “No migraine-with headache” groups. It was also found

that patients in the “No migraine-with headache” group had significantly lower puretone audiometry thresholds than patients in the “No migraine-without headache” group. Since the “Migraine” group in this study showed a lower rate of exhibiting MD-related symptoms except for vertigo compared to the “No migraine” groups, it is most likely that the “Migraine” and “No migraine” groups are associated with different pathologies.

The above findings support the inclusion of an objective method such as ECoChG to assist in the differentiation of MD and vestibular migraine, particularly as part of a test battery approach. This study’s first hypothesis was supported as a greater proportion of “negative” ECoChG cases were present in the “Migraine” group compared to the two “No migraine” groups. The different Gibson score and puretone hearing thresholds of the neural groups as discussed above suggest that a disease process other than MD may be present in the study population and support the study’s second hypothesis that patients with a history of migraine have characteristics which differ from patients without a history of migraine.

#### **4.2. Demographic Characteristics of Ménière's Disease**

The third hypothesis posed in this study was that the demographic characteristics of the patients with confirmed MD would fit within the range of demographic data published in previous papers. The present findings that the average age of first vertigo attack occurs between 50 and 60 years and that the patients ethnicities are evenly represented in the Canterbury population support this hypothesis. However, the finding that “clinically certain” MD was more common in males compared to females disagreed with this hypothesis.

In order to evaluate the demographic characteristics of MD, data from patients who met the criteria of “clinically significant MD” were analyzed and reported in the results section. In

recent years it has been reported that up to 33% of MD patients experience the onset of MD symptoms when they are aged 65 years or older (Shojaku et al., 2009), which is older than previously thought, the finding that the average age of vertigo onset in patients with “clinically significant MD” was 54 years therefore supports our third hypothesis as it is in line with recently published literature.

Males were over-represented in the “clinically significant MD” group. It has been generally reported in the literature that MD is either equally prevalent in males and females or slightly more prevalent in females (Havia et al., 2005; Shojaku et al. 2005). The inclusion of patients who were excluded from the main study group because they did not have a history of disequilibrium did not impact on the gender ratio of patients with “clinically significant MD”. Therefore, these results disagree with the current MD literature.

The majority of patients with “clinically certain MD” belong to the Caucasian ethnicity. This finding is consistent with the ethnic distribution of the Canterbury population during the time period from which the information was collected.

Demographic comparisons of vertigo age of onset between the three subject groups of “Migraine”, “No migraine-with headache”, and “No migraine-without headache” showed only a slight difference with the majority of patients first experiencing vertigo between 41-50, 51-60, or 61-70 years. The “Migraine” group had the earliest onset of vertigo (51.31 years), followed in order by the “No migraine-with headache” (52.13 years) and “No migraine-without headache” (54.45 years) groups. These findings provide limited support for the study’s second hypothesis as a similar pattern of vertigo onset is present for all the neural groups. This may be because MD and vestibular migraine have similar patterns of vertigo onset.

### **4.3. Findings of the Study in Relation to Previous Research**

While a number of epidemiological studies have explored the relationship between MD and migraine, very few studies have investigated the viability of using ECoChG to differentiate between these two disorders. As part of a wider study on the management of vestibular migraine, Johnson (1998) recorded electrocochleograms in patients diagnosed with vestibular migraine and found that five out of eight patients had positive ECoChG results. This finding led one author to warn against using ECoChG in the differentiation of MD and vestibular migraine (Shepard, 2006). In contrast, the current study results of 371 patients with vertigo suggests that ECoChG can assist in differential diagnosis, as patients with a history of migraine were found to have significantly higher rate of “ECoChG negative” occurrences.

A number of studies have used epidemiological data to show that there is a high co-occurrence of MD and migraine, with some authors suggesting that MD and migraine share an underlying pathology (Baier & Dieterich, 2009). Radtke et al. (2008) found that the frequency of migraine was twice as high in MD patients. Some authors have offered alternate explanations for the high comorbidity. For example, Lempert et al. (2009) suggested that the high rate of comorbidity could be partly attributed to vestibular migraine. The results from this current study support the suggestion that the co-occurrence of MD and migraine may have been overestimated in epidemiological studies as a result of vestibular migraine patients being falsely diagnosed with MD.

Comparisons of the demographic data of patients with MD, such as age of first vertigo onset and gender ratio, vary with data published from different populations. The demographic data on MD is widely varied with the reported prevalence ranging between 17 to 513 individuals per 100,000 (Havia et al., 2005; Watanabe et al., 1995; Wladislavosky-Waserman et al., 1982).

The wide variation in the literature may be attributable to a lack of consistency in the methodology used in the diagnosis of MD as well as an over-reliance on subjective measures of MD diagnosis as current estimations of prevalence are based on subjective measures such as the AAO-HNS CHE criteria. The reliability of prevalence estimations may be improved if objective measures were used to diagnose MD.

In this study, over one third of patients with “clinically certain” MD experienced their first attack of vertigo when they were aged 60 years or older, with the average age of vertigo onset of 54 years. This finding is consistent with current publications which indicate that MD onset is most common in 40 and 50 year-olds (Paparella, da Costa, Fox, & Yoo, 1991). These results also suggest that MD onset commonly occurs in individuals older than 60 years as was suggested by Shojaku et al. (2009).

The gender ratio of MD patients is generally accepted to be equal or slightly more common in females (Havia et al., 2005; Shojaku et al. 2005). However, the findings from this study and an earlier study by Kalin (2010) indicate that MD is more prevalent in males, with more than a third more males found in the study population to be diagnosed with “clinically certain MD” than females. There are several explanations for this finding, including the possibility that the Christchurch population somehow differs from previous population or that the data has somewhat been skewed by the different rates of men and women seeking medical attention. It is also possible that the presence of vestibular migraine patients in MD databases of these previous studies may be over-exaggerating the prevalence of MD among women.

#### **4.4. Clinical Implications**

The findings from this study have presented clinical implications for the future assessment of MD. Findings from comparisons of the ECoChG data, along with other characteristics of patients, between the three neural symptom groups, suggest that some patients with suspected MD may have been misdiagnosed and may instead have vestibular migraine. Differential diagnosis of these disorders through subjective measures can be very difficult as the symptoms of MD and vestibular migraine may overlap in some patients. Migraine disorders and MD require different management and treatments and as such patients who receive a misdiagnosis would be likely to receive less than optimal treatment. Findings from this study indicates that the use of physiological approach, such as ECoChG alongside the AAO-HNS CHE guidelines and Gibson score, may decrease the likelihood of a patient being given an inaccurate diagnosis.

#### **4.5. Limitations of the Study and Future Direction**

The population for this study was taken from patients who underwent ECoChG assessment at Christchurch Public Hospital, New Zealand. As the study population was localized to the wider Canterbury region, the results can only be used to accurately generalize to the Canterbury population. This study would have a larger degree of generalisation if it was extended to include medical records from other regions of the country.

Although this study reviewed a large number of medical records, the distribution of the sub-categories was uneven, with a relatively small number of patients assigned to the “No migraine-with headache” and “Migraine” groups. Consequently, the statistical tests of the smaller groups failed normality tests and nonparametric tests had to be used to analyse group

differences. In the future, it would be beneficial to examine data from a larger database to enhance the statistical power.

As this study has raised some interesting questions about the differentiation of MD and vestibular migraine, a large retrospective follow-up study is required to investigate the percentage of patients subjectively diagnosed with MD who actually have vestibular migraine. Future studies should also investigate the effectiveness of ECoChG assessment in providing correct diagnosis of MD and vestibular migraine. Research efforts aimed at combining subjective measures such as the AAO-HNS CHE and Gibson score with physiological tools such as ECoChG and MRI may maximise the sensitivity and specificity of the diagnosis.

#### **4.6. Conclusion**

It can be concluded that patients with MD-like symptoms are less likely to have a “positive” ECoChG finding if they have a history of migraine. Puretone audiogram and Gibson score data show that patients with suspected MD who have a history of migraine report symptoms which are significantly different from the symptoms reported by patients who have not experienced migraine. These findings imply that some people who experience MD-like symptoms may be experiencing vestibular migraine. Subjective criteria such as the AAO-HNS CHE would incorrectly diagnose such a patient as having MD. The differential diagnosis of MD and vestibular migraine is further confused in cases where patients with MD also happen to suffer from unrelated headaches. The inclusion of a migraine section in the AAO-HNS CHE criteria may improve the sensitivity and specificity of the AAO-HNS CHE criteria; however, unreliable reporting is still likely to cause difficulties. For this reason, it is important that patients are not diagnosed through subjective measures alone, particularly if they have a history of migraine attacks.



## Glossary

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### **COV**

A measure of relative variation; based on the standard deviation divided by the mean, expressed as a percentage.

$$CV = \frac{S}{\bar{X}} \times 100$$

### **Head-thrust Test**

A test in which patient is asked to fixate a stationary target while their head is moved short amplitude but very quickly horizontally.

### **Modified Hughson-Westlake “Ascending” Method**

A procedure for obtaining audiometric thresholds using a 5 dB step size where a tester decreases the stimulus presentation level by 10 dB if a response is given and increases the stimulus presentation level by 5 dB if no response is given.

### **Odds Ratio**

A measure of effect size, describing the strength of association or non-independence between two binary data values. The odds ratio is calculated as the odds of having a disease if exposed to a risk factor divided by the odds of having the disease if not exposed to the risk factor.

$$OR = \frac{a/c}{b/d}$$

### **Rinne Tuning Fork Test**

A test where a vibrating tuning fork is held against the mastoid process until the sound is lost and then brought close to the ear canal.

### **Romberg Test**

A test for the presence of Romberg's sign where a patient is asked to place their feet together and close their eyes.

### **Unterberger Stepping Test**

A test used to assess the vestibular system where a patient is asked to walk on the spot with their eyes closed.

### **Weber Tuning Fork Test**

A test where a vibrating tuning fork is held against the forehead and the patient is asked to report in which ear the sound is heard louder.

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## **Appendix 1 - Patients Without Confirmed Vertigo**

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Of the 24 patients excluded from the study because they lacked history of Ménière's type vertigo 37.5% were found to have "positive" ECoChG findings, indicating the presence of endolymphatic hydrops and therefore MD. The remaining 62.5% of patients were found to have "negative" ECoChG findings. The four females and five males with "positive" ECoChG findings are being monitored for the development of vertigo at the department of Otolaryngology of Christchurch Hospital (Christchurch, New Zealand).

## **Appendix 2 - Ethical Approval Forms**

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This study has been given ethical approval by the Chairperson and Deputy Chairperson of the Upper South A Regional Ethics Committee from the New Zealand Ministry of Health, Health and Disability Ethics Committees (URA/11/EXP/009) on 23 March 2011 and the University of Canterbury Human Ethics Committee (Ref: HEC 2011/04/LR) on 28 March 2011. The confidentiality of the participants in this study was carefully maintained and all participants were approached by the Otolaryngologist on the day of their ECoChG assessment and verbally consented to their otolaryngology and audiology files being used in MD research.

## **A2.1 Health Research Council Approval Letter:**

23 March

Ms Charlotte Giles  
Department of Communication Disorders  
University of Canterbury  
Private Bag 4800  
Christchurch

Dear Charlotte Giles,

**Ethics ref:** URA/11/EXP/009 (please quote in all correspondence)  
**Study title:** A demographic and instrumental study of Meniere's disease  
**Investigators:** C Giles, Prof J Hornibrook, Dr G O'Beirne, Dr E Lin (supervisor)

The above study has been given ethical approval by the Chairperson and Deputy Chairperson of the Upper South A Regional Ethics Committee.

### **Final Report**

The study is approved until **28 February 2012**. A final report is required at the end of the study and a report form to assist with this is available at <http://www.newhealth.govt.nz/ethicscommittees>. If the study will not be completed as advised, please forward a report form and an application for extension of ethical approval one month before the above date.

### **Amendments**

It is also a condition of approval that the Committee is advised if the study does not commence, or is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. The organisation may specify their own processes regarding notification or approval.

Yours sincerely



**Alieke Dierckx**  
Administrator  
Upper South A Regional Ethics Committee

## **A2.2 University of Canterbury Approval Letter:**

Ref: HEC 2011/04/LR

28 March 2011

Charlotte Giles  
Department of Communication Disorders  
UNIVERSITY OF CANTERBURY

Dear Charlotte

Thank you for forwarding to the Human Ethics Committee a copy of the low risk application you have recently made for your research proposal "A demographic and instrumental study of Ménière's Disease".

I am pleased to advise that this application has been reviewed and I confirm support of the Department's approval for this project.

With best wishes for your project.

Yours sincerely



Dr Michael Grimshaw  
***Chair, Human Ethics Committee***

## **Appendix 3 - Supplementary Information**

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### **A3.1 ECoChG Protocols and Procedures**

#### **A3.1.1 Recording the ECoChG**

The effect of acoustic stimulation on the patient's auditory system is measured via four electrodes at specific sites on the head. Surface electrodes are typically placed on the earlobes and forehead, while the active recording electrode is positioned as close to the cochlea as possible by placing it down the external auditory meatus prior to the placement of the headphone (Hall, 2007). These electrode positions correspond to Fp, A1 and A2 of the International 10-20 System of electrode placement (Jasper, 1958). The earlobe electrodes (A1 or A2) and the external auditory meatus electrode provide the differential recording, whilst the forehead electrode (Fp) is the ground electrode. Rubber bands attached to a ring shaped rubber bracket hold the recording electrode to position. An acoustic transducer (TDH-39 headphone) fits inside the bracket which is placed over the test patient's ear canal entrance allowing the acoustic stimuli to be transmitted to the ear (Hall, 2007).

#### **A3.1.2 Electrode Placement**

Two recording electrode placements are commonly used in ECoChG: transtympanic (TT) and extratympanic (ET). The TT ECoChG approach involves passing the recording electrode through the tympanic membrane and resting it on the promontory (Ferraro & Durrant, 2002). In TT ECoChG the recording needle electrode is close to the signal source which results in a robust

signal to noise ratio. Minimal signal averaging is required as the variability of TT ECoChG recordings is small. The time needed to generate a good waveform is also decreased by the TT ECoChG method.

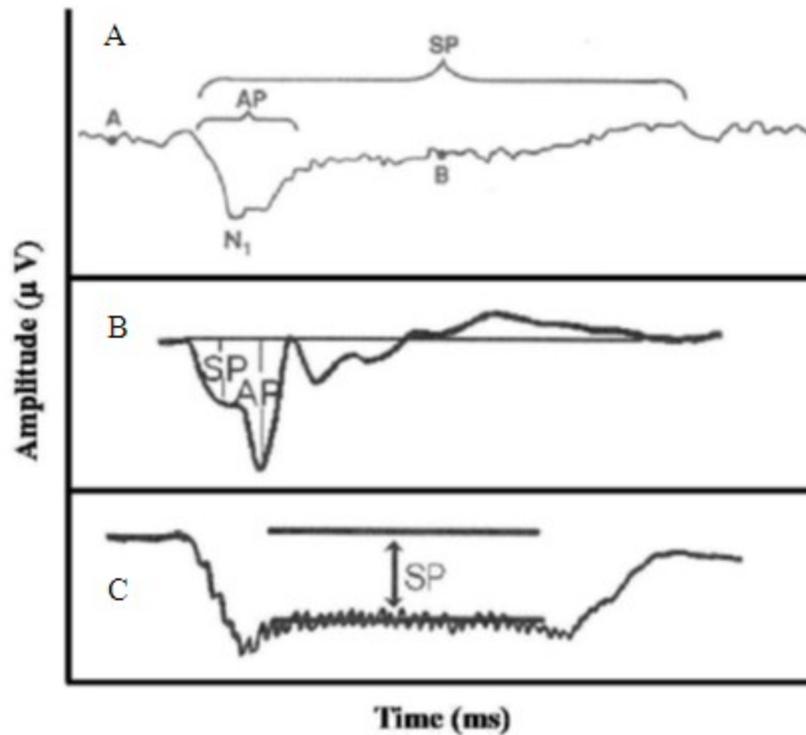
The TT ECoChG, however, has several limitations. Firstly, the procedure is relatively invasive and the needle piercing the tympanic membrane may cause the patient some discomfort even with local anesthesia. Secondly a physician must be present to place the electrode; as a result of this TT ECoChG is restricted to medical settings and comes at a greater cost. Extratympanic ECoChG is a less invasive technique where the electrode sits on the tympanic membrane or against the skin of the external auditory meatus (Bohlen, Arenberg & Gibson, 1990; Ferraro & Durrant, 2002). The advantages of this technique are improved patient comfort and improved affordability as the complete procedure can be carried out by a suitably trained person rather than a physician. Using ET ECoChG however, compromises the quality and reproducibility of the waveforms. The signals recorded from this more distant location require more signal averaging, have lower magnitude and poorer signal to noise ratio all of which means that interpretation of the waveform becomes more difficult.

### **A3.1.3 Stimuli Type**

Click and tone burst stimuli of varying intensities are played to elicit ECoChG responses (Hall, 2007). Both clicks and tone bursts have an important role in recording auditory evoked responses (AERs) however, each stimulus also has inherent advantages and disadvantages. Clicks were the first acoustic stimuli to be used for ECoChG clinically. Clicks evoke a clear action potential due to their sharp onset but can cause distortion of the SP waveform and acoustic ringing. Tone bursts which were originally described in 1974 by Eggermont and Odenthal (cited

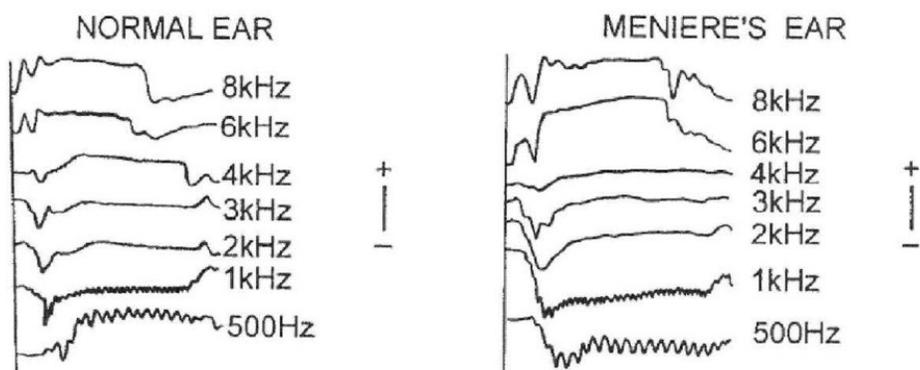
in Gibson, 1994), to measure the absolute SP amplitude at different frequencies. They differ from clicks as they have a more gradual onset and longer duration which elicits a slightly less clear response. However, the frequency specificity and longer duration of tone bursts, enables improved differentiation between SP and AP allowing focus on specific areas of the cochlea which may be affected by MD (Gibson, 1991). Tone bursts were initially dismissed by Eggermont and Odenthal who reported they have little clinical value, however tone bursts are now considered to be the more clinically useful of the two stimuli.

The clinical value of tone bursts and click stimuli have been compared in several publications. A study by Gibson (1993) demonstrated higher accuracy in the detection of MD when using a 1 kHz tone burst, compared with the accuracy achieved with a click stimulus. Another study by Gibson compared click and tone burst stimuli in 1,101 patient ears and found that click and 4 kHz tone burst stimuli gave the poorest diagnosis of MD. This study also suggested that 1 kHz tone burst was twice as effective click stimulus, except in ears in ears which are missing a large number of hair cells (patients hearing thresholds exceed 60dBHL) (Gibson, 1994). These findings from Gibson were supported by Ge and Shea (2002) who recorded transtympanic (TT) electrocochleograms in 2,421 ears using click and tone bursts and concluded that tone bursts are the more useful stimulus due to their frequency specificity. In practice the examiner would use click and tone burst stimuli to obtain a more complete clinical picture. Figure 9 shows the ECoChG waveforms evoked by click and tone burst stimuli.



**Figure 9:** ECoChG waveforms evoked by clicks and tone bursts. A) an ECoChG recording in response to a 2 kHz tone burst in an ear without endolymphatic hydrops (copied from Kalin, 2010 (originally from Ferraro, 2000; p. 436), B) a diagram of the response to a click stimulus and C) response to a tone burst stimulus in an ear with endolymphatic hydrops (taken from Kalin, 2010 (originally from Gibson, 2009; p. 39).

The polarity of the SP elicited from tone burst stimuli has been shown to change at different frequencies, presumably due to the geometry of the cochlear. As demonstrated in Figure 10, the SP of normal ears is positive at 500Hz, slightly negative at 2 and 1 kHz, neutral at 3 and 4 kHz and positive at 8 kHz. Gibson (1996) suggested that 1 kHz is the most useful frequency for the detection of endolymphatic hydrops.



**Figure 10:** The SP waveforms in response to a 90 dB HL stimulus at different frequencies in a normal ear (left) and in a MD ear (right) (taken from Kalin, 2010 (originally from Gibson, 1996; p. 14).

### A3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a neuroimaging technique used to diagnose and evaluate inner ear diseases. The small size of the inner ear has until recently meant that the inner ear could not be visualized in vivo however, recent advances of MRI with gadolinium (Gd) injection have allowed the visualization of ultrastructural details of the inner ear. As a result of the small amount of time researchers have had access to this technology, most of what we currently know about inner ear pathology has been derived from post-mortem histology rather than MRI (Hornibrook, Coates, Goh & Bird, 2010 ; Pyykkö et al., 2010). Under the AAO-HNS CHE guidelines patients with suspected MD may only be diagnosed with “certain” MD when endolymphatic hydrops is identified at post mortem. However, MRI use is rapidly increasing as the technology sees improves in magnetic strength and image sequencing and as the cost-effectiveness of this tool increases. MRI scanning of the inner ear is an exciting new

development in the diagnosis of MD and other inner ear disorders. It is now being used to assist in the diagnosis of disorders MD through the visualization endolymphatic hydrops (Nakashima et al., 2007). A grading system has been developed to classify temporal bone images as wither “none”, “mild” or “significant” in terms of endolymphatic hydrops (Nakashima et al., 2009).

**Table 7:** The grading system of temporal bone images from MRI (taken from Nakashima et al., 2009).

| Grade of<br>hydrops | Vestibule<br>(area ratio*) | Cochlea   |
|---------------------|----------------------------|---|
| None                | $\leq 33.3\%$              | No displacement of Reissner’s membrane  |
| Mild                | $>33.3\%, \leq 50\%$       | Displacement of Reissner’s membrane<br>Area of cochlear duct $\leq$ area of the scala vestibuli |
| Significant         | $>50\%$                    | Area of the cochlear duct exceeds the area of the<br>scala vestibuli                            |

\*Ratio of the area of the endolymphatic space to that of the fluid space (sum of the endolymphatic and perilymphatic spaces) in the vestibule measured on tracings of images.

With further research MRI may soon enable a “certain” diagnosis under the AAO-HNS CHE guidelines in vivo. MRI may also prove useful in differentiating between migraine and MD. If the vertigo attacks experienced by patients with migraine are an entirely different entity

to endolymphatic hydrops and MD then migraine patients should receive a low grade, on the afore mentioned scale.

A number of studies have compared MRI to other assessments of MD. Fiorino et al. (2011) found no clear correlation between MRI images and clinical history or ECochG, the only statistically significant correlation was with VEMPs. Further research is now required to delineate the role of MRI in the diagnosis and management of MD (Hornibrook et al., 2010).

### **A3.2 AAO-HNS Criteria History**

The original 1972 guidelines used a letter designation system to categorize the patient symptoms based on the consistency of the presence of vertigo episodes in relation to hearing status (Committee on Hearing and Equilibrium, 1985). The AAO-HNS CHE integrated a formula into the 1985 guidelines to improve the accuracy of the diagnosis. Each subsequent publication of the AAO-NHS guidelines has evolved from earlier editions allowing the conservation of existing data. The current 1995 edition of the AAO-NHS CHE guidelines assign MD patients into four diagnostic levels: “possible”, “probable”, “definite”, and “certain” (Members of the Committee on Hearing and Equilibrium, 1995). Van de Heyning et al. (1997) compared the 1995 AAO-HNS CHE criteria with different diagnostic approach called the Inner Ear Profile. The Inner Ear Profile quantifies cochlear symptoms for each ear and vestibular symptoms through sets of scales from 0 to VI. In contrast to the AAO-HNS CHE criteria, the Inner Ear Profile is applicable to several inner ear disorders, while the AAO-HNS guidelines restrict themselves to the graded diagnosis of MD. Van de Heyning et al. (1997) concluded that the AAO-HNS CHE criteria is the more restrictive of the two methods as MD is the only possible diagnosis even if the patient has another disorder with similar symptoms. On the

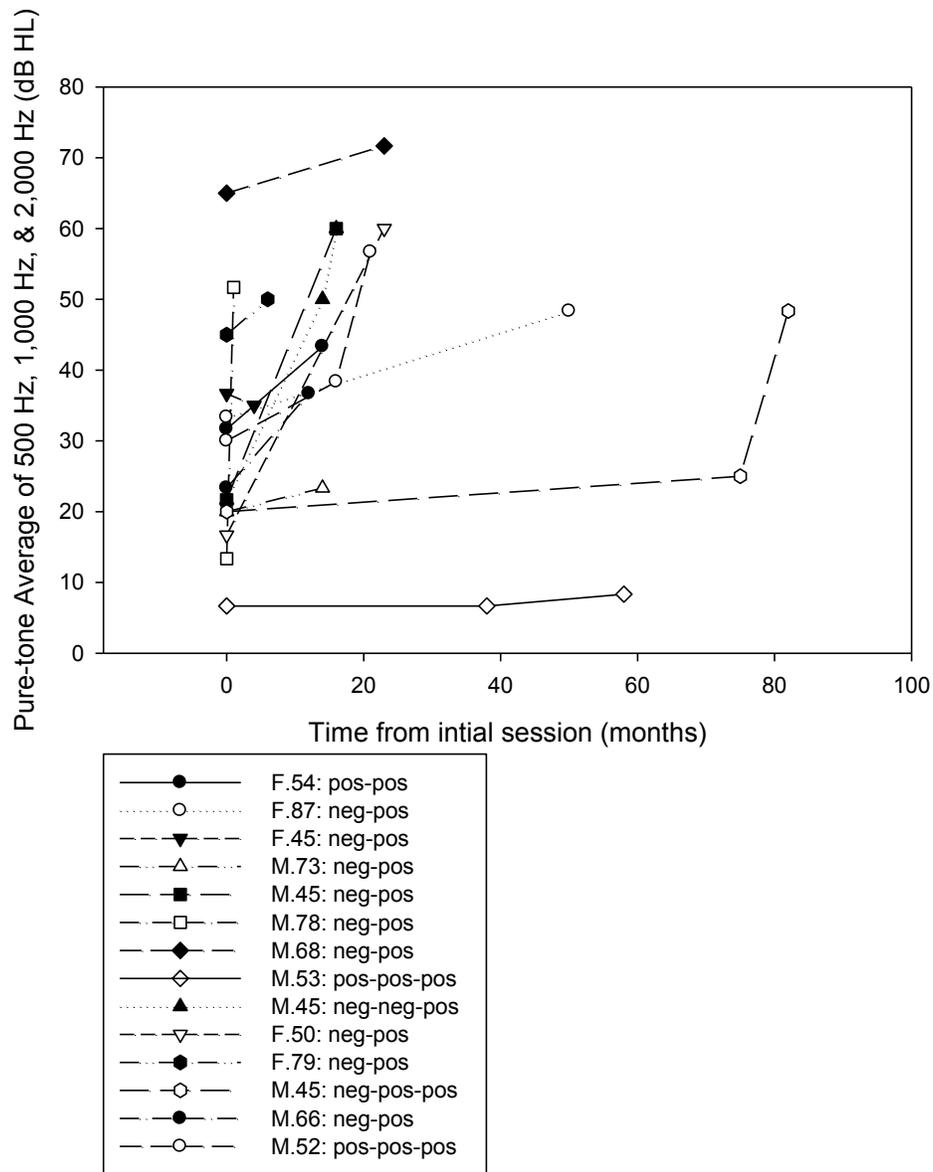
contrary the Inner Ear Profile provides an accurate description of the patient condition before a definite diagnosis is made. The AAO-HNS CHE criterion also provides a more superficial description of the main symptoms, for example the duration of the vertigo attacks and the severity of the tinnitus and aural pressure are not taken into account. The Inner Ear Profile is able to describe the disability of hearing loss and its effect on the individual, whilst the AAO-HNS CHE does not address the impact of disability. The authors concluded that developing a unified method by adapting the Inner Ear Profile to the 1995 AAO-HNS CHE guidelines may provide a more effective diagnostic approach for MD through the integration of grades of tinnitus, pressure and imbalance.

## Appendix 4 - Supplementary Results

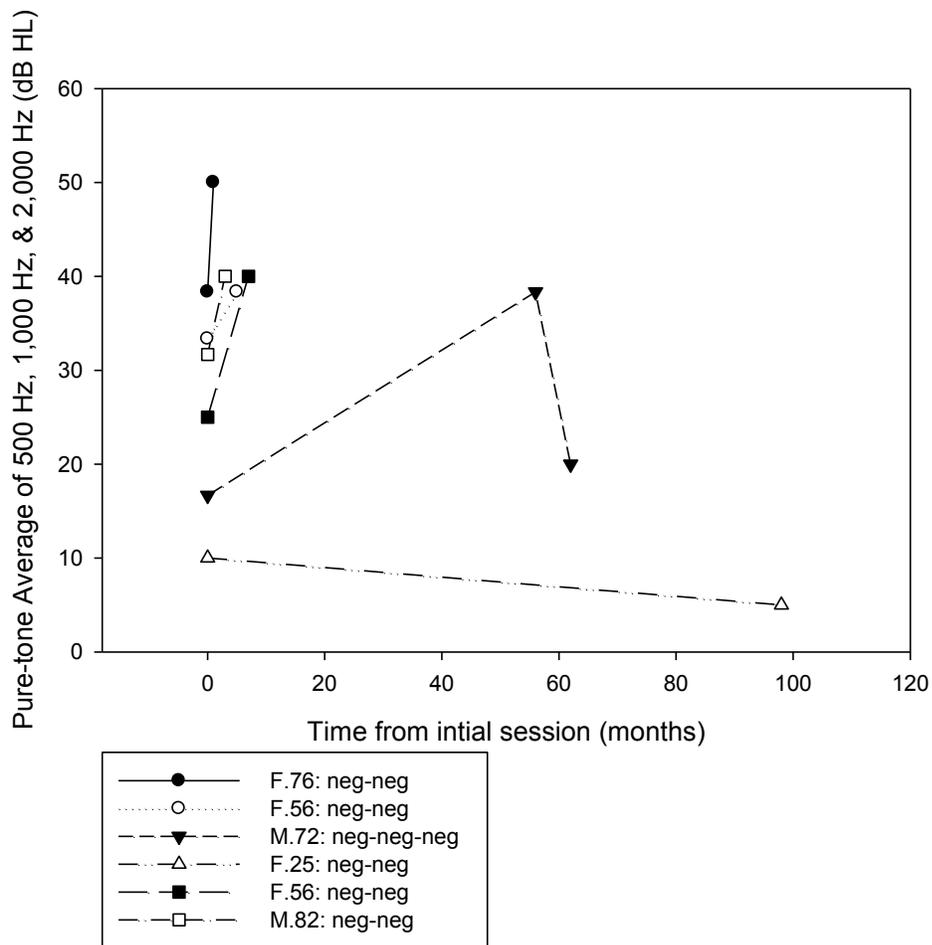
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### A4.1 Progression of Hearing Loss over Time

Figure 11 shows the progression of hearing loss (defined as the average audiometric threshold at 0.5, 1, and 2 kHz of the poorer hearing ear), and the ECoChG findings of patients who were identified as having a “positive” ECoChG result at their last ECoChG assessment. The hearing loss progression of patients who had a “negative” ECoChG result more recently are shown in Figure 12. For patients identified as “positive” at their most recent ECoChG assessment, all but one of them showed a worsening of hearing levels over time, with the length of the observation period ranging from 1 to 82 months. The extent of hearing deterioration ranged from 2 to 43 dB HL (puretone average of 500 Hz, 1 kHz and 2 kHz) in females (Mean = 12.5, SD = 16.321) and from 2 to 38 in males (Mean = 21.667, SD = 15.546). No significant gender difference was found on the extent of hearing loss for these “positive” cases ( $t = -1.097$  df = 13,  $p = 0.292$ ). Of the six patients identified as having a “negative” ECoChG at their most recent assessment, five patients showed a worsening in hearing levels, with the extent of hearing deterioration ranging from 3 to 15 dB HL (Mean = 10.9524, SD = 13.6713), while one patient showed a slight improvement in hearing thresholds.



**Figure 11:** Hearing loss (Pure-tone Average) and ECoChG progression over time in patients with “positive” ECoChG findings at their most recent assessment. Patient age, gender and ECoChG finding are displayed in the legend box (e.g., “M.73: neg-neg-pos” means the patient is a 73 year-old male who was diagnosed as “negative” on the first two visits with ECoChG measures and “positive” on his third visit).



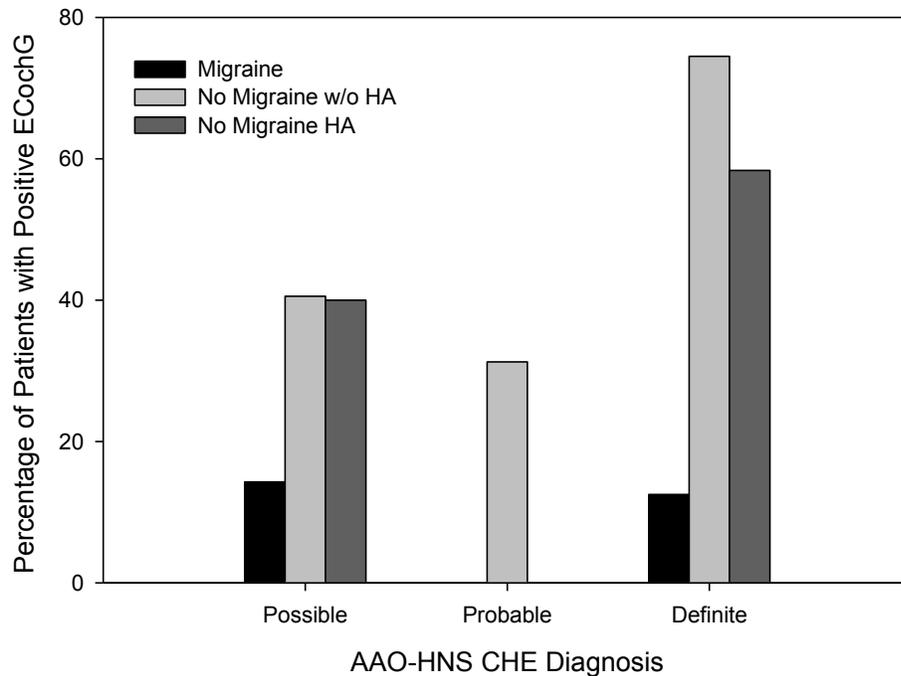
**Figure 12:** Hearing loss (Pure-tone Average) and ECoChG progression over time in patients with “negative” ECoChG findings at their most recent assessment. Patient age, gender and ECoChG finding are displayed in the legend box (e.g., F.76: neg-neg” means the patient is a 76 year-old female who was diagnosed as “negative” with ECoChG measures at two assessments).

## **A4.2 Subjective Test Results**

### **A4.2.1 AAO-HNS CHE Criteria in the Presence of Neural Symptoms**

In Figure 13, the ECoChG findings and AAO-HNS CHE diagnosis of the patients are compared between the three patient groups based on neural symptoms. The AAO-HNS CHE guidelines are sub-categorized into four categories called “possible MD”, “probable MD”, “definite MD” or “certain MD”. There was a significant difference in the distribution of the three neural symptom groups (“Migraine”, “No migraine-with headache” and “No migraine-without headache), within the “Possible MD” (chi-square = 129.732, df = 2, p = 0.000), “Probable MD” (chi-square = 13.235, df = 1, p = 0.000) and “Definite MD” groups (chi-square = 312.604, df = 2, p = 0.000). Results of nonparametric tests revealed that there were significantly more “negative” than “positive” ECoChG cases in the “Possible MD” group (chi-square = 10.169, df = 1, p = 0.001) but more “positive” than “negative” identifications in the “Definite MD” group (chi-square = 38.208, df = 1, p = 0.000). There was also no significant difference between the number of “positive” and “negative” identifications in the “Probable MD” group (chi-square = 2.882, df = 1, p = 0.09).

The prevalence of “positive” identifications was significantly higher in the “Definite MD” group than both the “Possible MD” (chi-square = 40.234, df = 1, p < 0.001) and “Probable MD” groups (chi-square = 10.819, df = 1, p = 0.001), which were not significantly different from each other (chi-square = 0.101, df = 1, p = 0.750). In patients with a “positive” ECoChG identification the distribution of the “possible MD” (chi-square = 66.269, df = 2, p = 0.000) and “definite MD” groups (chi-square = 256.265, df = 2, p = 0.000) were found to be significantly related to the neural group of the patients.



**Figure 13:** The percentage of “positive” ECoChG findings and the AAO-HNS CHE diagnosis of participants with a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”).

Patients categorised as having “definite MD” were shown to have a large percentage of “positive” ECoChG results in the “No migraine-without headache” and “No migraine-with headache” groups of patients while the “possible MD” patients were shown to have more “negative” ECoChG results in these groups of patients. Patients with “Migraine” had a very low percentage of “positive” ECoChG results. The percentages of “possible MD” and “definite MD” cases were relatively similar in the “Migraine” patients, with a slightly high percentage of

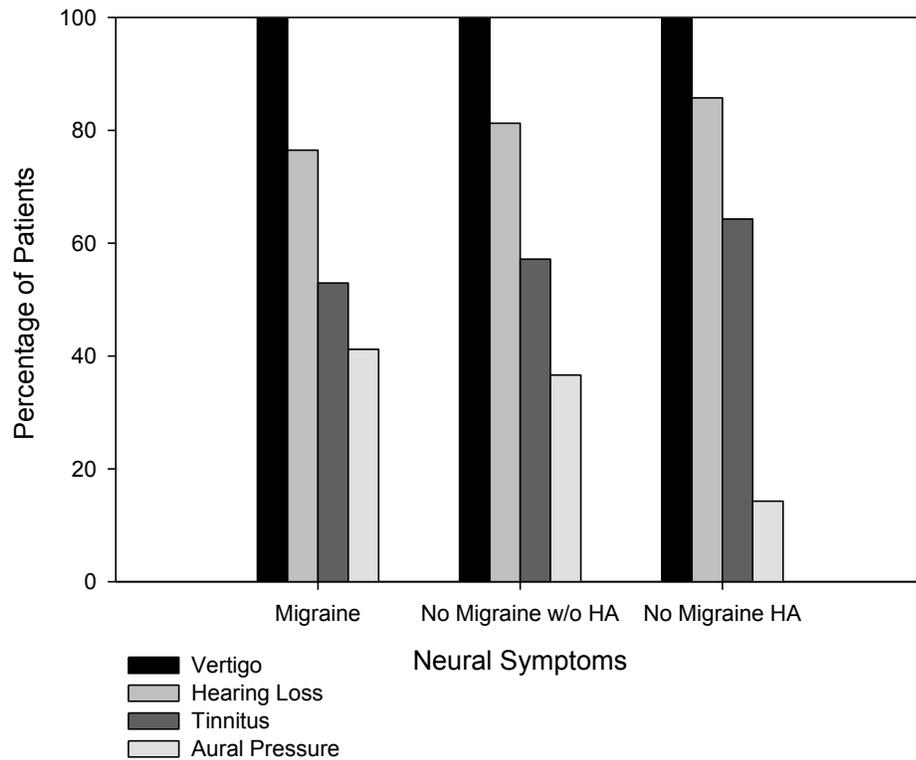
“positive” ECoChG in “possible MD” cases. Patients with “no migraine-with headache” and “probable MD” were found to have a low percentage of “positive” ECoChG results. No “Migraine” or “No migraine-without headache” patients were found to have “probable MD” and “positive” ECoChG results.

#### **A4.2.2 Relationships between Symptoms**

Figure 14 shows the relationship between vertigo, hearing loss, tinnitus, and aural pressure in patients with a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”). Hearing loss was the most common symptom in all the groups of patients, followed by, tinnitus and then aural pressure (Vertigo was an inclusion criterion for all patients). Hearing loss and tinnitus were the least common symptoms in “Migraine” patients and most prevalent in “No migraine-with headache” patients. Conversely aural pressure was most common in “Migraine” patients and least common in patients with “No migraine-with headache”.

Results of nonparametric tests revealed that revealed that in all of the groups “hearing loss” is significantly more common than “no hearing loss” “Migraine” group (chi-square = 4.765, df = 1, p = 0.029), “No migraine-without headache” group (chi-square = 43.75, df = 1, p = 0.000) and “No migraine-with headache (chi-square = 7.143, df = 1, p = 0.008). No significant differences in hearing loss were found between the groups. The symptom “tinnitus” was not significantly more common than “no tinnitus” in the groups and no significant differences in the presence of tinnitus were found between the groups. Nonparametric tests showed that patients were significantly more likely to have “no aural fullness” than “aural fullness” in the “No

migraine-without headache (chi-square = 8.036, df = 1, p = 0.005) and “No migraine-with headache groups (chi-square = 7.143, df = 1, p = 0.008), while no significant difference was present in the “Migraine” group (chi-square = 0.529, df = 1, p = 0.467). No significant differences in aural fullness were detected between the groups.



**Figure 14:** The percentage of patients with documented symptoms of vertigo, hearing loss, tinnitus and aural pressure in patients with a history of migraine (“Migraine”), patients who had no history of migraine and who were with (“No migraine-with headache”) or without reported headaches with attacks of vertigo (“No migraine-without headache”).

## Appendix 5 – Appendix References

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