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Association of White Matter Hyperintensities in Patients with Sudden Sensorineural Hearing Loss and Migraine Headaches

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TABLE OF CONTENTS

Page

LIST OF FIGURES.....iii

LIST OF TABLES.....iv

ACKNOWLEDGMENTS.....v

ABSTRACT.....vi

CHAPTER 1: INTRODUCTION.....1-6

CHAPTER 2: BACKGROUND.....7-18

CHAPTER 3: METHODS.....19-22

CHAPTER 4: RESULTS.....23-26

CHAPTER 5: DISCUSSION.....27-30

CHAPTER 6: CONCLUSION.....31-32

REFERENCES.....33-35

LIST OF FIGURES

		Page
Figure 1.1	A 35-year old woman with severe SSNHL in her left ear	11
Figure 1.2	Representative axial FLAIR images of WMHs	13
Figure 1.3	Brain Magnetic Resonance T2-Weighted MRI at Baseline and Follow-up	16
Figure 2.1	Fazekas Grading Scale on T2-Weighted MRI Scans with PVH Lesions	21
Figure 2.2	Fazekas Grading Scale on T2/FLAIR MRI Scans with DWMH Lesions	21
Figure 3.1	Distribution of White Matter Hyperintensities for Control and Sudden Hearing Loss Subjects Based on Fazekas Scale	23
Figure 3.2	Distribution of White Matter Hyperintensities for Control and Sudden Hearing Loss Subjects Based on Mirsen Scale	24
Figure 3.3	Distribution of White Matter Hyperintensities for Subjects with Both Migraine and Sudden Hearing Loss Diagnosis Based on Fazekas Scale	25
Figure 3.4	Distribution of Deep White Matter Hyperintensities for Subjects with Both Migraine and Sudden Hearing Loss Diagnosis Based on Mirsen Scale	25

LIST OF TABLES

Page

Table 3.1 Count of White Matter Hyperintensities Based on Fazekas Grading Scale 23

Table 3.2 Count of White Matter Hyperintensities Based on Fazekas Grading Scale 24

Table 3.3 Mean Fazekas and Mirsen PVH and DWMH Grading Scores 26

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ABSTRACT

Association of White Matter Hyperintensities in Patients with Sudden Hearing Loss and Migraine Headaches

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Sudden sensorineural hearing loss is a debilitating disorder characterized by a rapid loss of hearing within a short period of time due to damage to the cochlea. This medical emergency is most often attributed to infectious, vascular, traumatic, and autoimmune causes. However, another potential cause of sudden hearing loss is migraine headaches.

In order to further investigate the association of migraine in cases of sudden hearing loss, we looked at T2-weighted MRI sequences of normal healthy adults, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis. Specifically, we looked at white matter hyperintensities on T2-weighted MRI scans of all the respective subjects by using the Fazekas and Mirsen scale to grade deep and periventricular white matter hyperintensities.

Our work showed a possible link between migraines and sudden hearing loss because subjects in these respective groups consistently showed similarities in the abnormalities seen on their MRI scans. Therefore, our work suggests a possible link amongst the two illnesses, which helps in the development of better treatment options for patients with this debilitating disorder.

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a startling symptom characterized by a rapid loss of hearing within a short period of time due to damage to the cochlea or auditory nerve. ISSNHL is typically defined as an unexplained sensorineural hearing loss greater than 30 decibels in three consecutive audiometric frequencies that occurs over a 72-hour period. Although any age group can be affected, most individuals affected by the disorder are between 43 to 53 years of age, with equal sex distribution. ISSNHL has an estimated incidence between 5 and 20 per 100,000 persons per year; however, this is likely an underestimate because many individuals who recover quickly never seek attention from a medical professional [1]. Most cases of ISSNHL are unilateral and less than two percent of patients have bilateral involvement, which is sequential. Some of the accompanying symptoms of the illness frequently include tinnitus and dizziness.

Sudden sensorineural hearing loss is a relatively common condition in otologic and audiologic practices. Approximately, for seven to 45 percent of patients, a defined cause can be found and a specific treatment protocol can be used. The vast majority of patients, however, with SSNHL are classified as idiopathic because they have no identifiable cause for the hearing loss. Despite advances in research, controversy remains regarding the etiology of the disorder. Some of the identifiable etiologies of SSNHL fall into the following broad categories: infectious, vascular, traumatic, autoimmune, and other. For many of these identifiable etiologies, the hearing loss results from damage to the hair or other cochlear structures.

The etiology of the majority of patients with SSNHL is unknown, thus many hypotheses of idiopathic SSNHL have been proposed. One etiologic hypothesis for ISSNHL is

the infectious theory in which authors propose that a viral infection in the inner ear causes cochlear inflammation or damage to inner ear structures. Data from clinical, animal, and temporal bone human studies have provided evidence to support this etiology. High levels of serum antiviral antibodies have been isolated from the serum of patients suffering from idiopathic SSNHL such as herpes zoster, herpes simplex type 1, influenza B, mumps, enterovirus, cytomegalovirus, and rubeola. In addition, temporal bones from patients with idiopathic SSNHL show "histological patterns similar to those seen in viral labrinthitis including atrophy of the organ of corti, tectorial membrane, stria vascularis, and vestibular end organ." The viral etiology of ISSNHL has also been supported by animal experiments where applying the simplex type 1 virus to the round window in guinea pigs induced sensorineural hearing loss [2]. Nonetheless, although antiviral drugs, acyclovir and valacyclovir, have been used to treat SSNHL as a result of this theory, the published clinical studies that used these drugs did not show any benefit for the treatment of ISSNHL [3, 4].

Another etiologic hypothesis for ISSNHL is the vascular theory. According to the vascular theory, the sudden hearing loss could result from acute vascular hemorrhage, vascular disease, occlusion by emboli, vasospasm, or change in blood viscosity. The theory arises by the fact that the blood supply to the cochlea occurs from small terminal arteries. For example, the labyrinth artery is an artery at the end that carries red blood cells and oxygen into the inner ear; therefore, tissue injury may result due to oxygen deprivation and ischemia within seconds in the cochlea [5]. The labyrinth artery is very vulnerable to blood pressure oscillation and abnormalities in blood flow. The low blood flow may cause anoxia due to hyperviscosity, and this results in cochlear hypofunction and inability to maintain cochlear metabolism [6]. Nonetheless, most cases of SSNHL are not consistent with a

vascular etiology because in cases where the hearing loss results from a known intravascular injury, the loss is often permanent. However, in the majority of cases of idiopathic SSNHL, the hearing loss is often reversible. Additionally, cochlear fibrosis is typically not observed in idiopathic SSNHL; thus, vascular etiology may explain some but not most cases of ISSNHL [2]. Although many different treatments exist for ISSNHL that have been developed in response to the vascular theory such as dextran infusion, hyperbaric oxygen, pentoxifylline, fibrogen aphersis, and Rheopheresis, there is clinical research evidence both to support and refute such treatments [7-11].

A third possible etiologic hypothesis for ISSNHL is cochlear trauma with tearing of the delicate inner ear membranes. Previous studies have reported several patients who complained of hearing a popping sound during the onset of their sudden hearing loss and proposed that the Reissner's membrane was the site of injury. Essentially, the rupture of the oval or round window causes loss of the perilymph and results in pressure alteration between the chambers that contain perilymph and endolymph. Due to this theory, surgery has been used with the intention to repair oval or round window perilymph fistulae for treatment purposes for patients with ISSNHL. However, there is evidence that argues against this theory since not all temporal bone studies have found evidence of active or healed ruptures of oval/round window, basilar membrane, or Reissner's membrane [12-14].

Lastly, another potential cause of ISSNHL is autoimmunity based on clinical data and pathological findings from autoimmune tests. Some hypothesize that hearing loss may be a consequence of local autoimmune processes within the inner ear or autoimmune diseases. The immunologic theory is supported by the presence of antibodies against antigens in the inner ear as well as the formation of immune complexes in the stria vascularis,

endolymphatic sac, and ducts. Ultimately, autoimmunity can cause damage to the cellular components of the organ of Corti, affect the stria vascularis, create dysfunction of the endothelial cells/fibrocytes, impair diffusion of potassium to the endolymph fluid, and affect the supporting cells of the organ of Corti [15-17]. It has been speculated that due to the improvement of patients with SSNHL following the use of adrenocorticotropic hormone, its etiology should be an autoimmune vasculitis. Furthermore, many cases of ISSNHL have been successfully treated by immune suppressive therapy, which reinforces the existence of immune-mediated mechanisms for the pathophysiology of SSNHL [18]. Nonetheless, although the treatment of ISSNHL with corticosteroids was a result of the immunologic theory, some studies on the impact of corticosteroids on SSNHL show contradictory results [19-22].

Objective

Sudden hearing loss is most often attributed to infectious, vascular, traumatic, and autoimmune causes but another potential cause of ISSNHL is migraine headaches. Although migraines as a cause for sudden hearing loss is not yet accepted by the scientific community, many unexplained cases of sudden hearing loss meet the diagnostic criteria for migraine with other neurologic phenomena. In a case study done to explore the relationship between migraines and sudden hearing loss, thirteen patients reported migraine headaches beginning in childhood prior to the hearing loss. The typical sequence of symptoms of the patients was migraine headaches followed by hearing loss followed by vertigo [23]. Even though a history of migraine is not considered to be a risk factor for SSNHL, it has not been thoroughly investigated. Some case reports have indicated that patients with SSNHL also

experience other symptoms attributed to migraine. Additionally, sudden hearing loss associated with severe migraines may be associated with ischemic changes in the inner ear. When researchers used a large study investigating the association between migraine and the incidence of SSNHL over a 10 year period using the National Health insurance Research Database in Taiwan, a universal health care system with centralized information on all diagnostic codes and prescriptions. The study designed a case control study with incidence of SSNHL in migraine patients and control subjects. There were a total of 10,280 migraine subjects and 41,120 control subjects, who were followed for an average of five years until the subject either developed SSNHL, died, or the study ended. The authors reported a 1.8 fold increased risk of SSNHL in patients with migraine [24].

In another study, researchers investigated the proportion of SSNHL patients in a representative population cohort with migraine. They studied a national sample cohort from the Korean National Health Insurance Service, where data was collected from 2002 to 2013. A total of 45,114 migraine participants were matched according to "age, sex, income, region of residence, hypertension, diabetes, dyslipidemia" with 180,456 controls. Of the total patients, 0.9% of the migraine patients and 0.6% of the controls were diagnosed with SSNHL. Overall, the study provided strong evidence that migraine patients had a higher likelihood of SSNHL [25].

In order to further investigate the association of migraine in cases of sudden hearing loss, we looked at T2-weighted MRI sequences of normal healthy adults, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis. Specifically, we looked at white matter hyperintensities on T2-weighted MRI scans of all the respective subjects. White matter hyperintensities are typically a common finding on MRI in older subjects and

in patients with dementia or stroke. Although in the past, WMH were generally dismissed as an inevitable consequence of normal aging, their prevalence is highly variable and numerous studies indicate that they have important clinical and risk factor associations. WMH are clinically important biomarkers, and they are also associated with brain damage such as global atrophy and other features of small vessel brain damage, with focal progressive visible brain damage. Thus, when physicians are making clinical diagnoses, which likely represent a mixture of pathologies, they ought to focus on intermediary markers of brain damage, such as WMH, which often reflect specific pathologic mechanisms [26]. Therefore, by viewing WMH on the T2- weighted MRI scans of normal healthy adults, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis, we were able to compare the structural abnormalities seen on each respective patient population. By comparing the T2-weighted images, we observed the association between sudden hearing loss and migraine headaches on a structural level. If structural similarities are found between the respective subjects, a link amongst the two illnesses could possibly be made, which would aid in the development of better treatment options for patients with the disorder.

CHAPTER 1

BACKGROUND

1.1 *Auditory System*

The auditory system is composed of two subsystems, the peripheral and central system. The peripheral auditory system is comprised of the outer, middle, and inner ear, and the central auditory system is composed of the auditory pathways and auditory cortex. The primary function of the outer ear is to collect and direct the sound waves that are traveling through the air into the ear canal and transmit the sound waves to the tympanic membrane. Moreover, the middle ear consists of the tympanic membrane and ossicular chain. Ultimately, the movements of the tympanic membrane set the malleus, incus, and stapes into motion. The stapedius and tensor tympani muscles are attached to the ossicular chain, and the contractions of these muscles reduce the intensity of sound transmission to the inner ear. Furthermore, the inner ear is comprised of two functional systems, cochlea and the vestibular system. The cochlea receives sound in the form of vibrations, which cause the stereocilia to move. The stereocilia then converts these vibrations into neural message, and these messages are passed to the auditory nerve and carried up to the brain [27-28].

1.2 *Hearing Impairment*

Hearing loss is typically classified into four categories: conductive, sensorineural, mixed, and central. Conductive hearing loss is often caused by difficulties in the transmission of sound into the inner ear. Usually, physicians make a diagnosis for conductive hearing loss by observing the air-bone gap on an audiometry, which should be more than 10 dB. The audiometry should indicate that hearing is better when sound is transmitted by a means where it bypasses the middle ear ossicular chain. Furthermore, sensorineural hearing loss

occurs without an air-bone gap because ear conduction is considered equal to bone conduction. Once again, a diagnosis for sensorineural hearing loss is also made through audiometry. Patients with the cochlear damage have no Otoacoustic Emissions testing, and patients with auditory nerve damage fail the Brainstem Auditory Evoked Responses-testing. Mixed hearing loss is simply a combination of conductive hearing loss and sensorineural hearing loss. Moreover, central hearing loss occurs due to damage to the central pathways. Because the diagnosis for central hearing loss can not be made by pure tone audiometry, patients with this type of hearing impairment have poor scores of word recognition and speech reception [29].

1.3 *White Matter Hyperintensities and T2-Weighted MRI*

White matter hyperintensities (WMH) are common findings on T2-weighted and fluid attenuated inversion recovery(FLAIR) brain MRI, particularly, in elderly cohorts. The majority of WMH lesions are in the periventricular white matter and deep white matter spaces. The signal on the T2-weighted images depends on the local concentration of water in interstitial spaces. Current findings suggest that WMHs have a deleterious effect on cognition, and some studies suggest that periventricular white matter affect neuropsychological performances. At the tissue level, "WMH associated damage ranges from slight disentanglement of the matrix, enlarged perivascular spaces due to lack of drainage of interstitial fluid and, in severe cases, irreversible myelin and axonal loss." Among these lesions, demyelination of myelin most frequently happens in old age and may take place long before the emergence of cognitive or affective symptoms [30].

Although WMHs were previously regarded as an incidental finding with no

therapeutic consequences, it is becoming clearer that WMHs are associated with cognitive decline in attention, executive function, and process speed domains. Due to its clinical relevance, there has been growing interest in white matter changes, there pathology, epidemiology, risk factors, and treatment options. For example, one study looked at the definite lesion and pathophysiology that leads to cognitive dysfunction in patients with infratentorial stroke, and the results from the research study suggested that the impairment of cognitive function in patients with infratentorial stroke seemed to be associated with subcortical white matter changes. In addition, the performance on the neuropsychological test of patients with WMH group was inferior to the no-WMH group throughout the cognitive function domain [31]. Therefore, WMH may be an important aspect of T2-weighted MRI scans to study risk factors of illnesses such as sudden sensorineural hearing loss.

1.4 *Idiopathic Sudden Sensorineural Hearing Loss and White Matter Hyperintensities*

Even though the exact etiology of sudden sensorineural hearing loss(SSNHL) is still debated, research studies have shown that lesions invading inner ear structures may be an identifiable cause leading to secondary sudden hearing loss. "Approximately 1-6% of patients with SSNHL show vestibular Schwannoma (VS) on magnetic resonance imaging, which is known as the most common finding in SSNHL with inner ear lesions." Thus, research suggests that MRI scans of patients could potentially provide valuable information to predict the prognosis and diagnostic process of SSNHL when lesions are suspected because clinical characteristics may differ amongst the patients [32].

In another research study, white matter hyperintensities in T2-weighted images in periventricular regions have been shown to be markers of cerebral small vessel disease. These hyperintensities , in periventricular white matter, increase with age and occur with cardiovascular risk factors such as high/variable blood pressure, pulse pressure, and ultrasound measures of common carotid artery diameter. Previous studies have illustrated that periventricular WMH in post-mortem tissue from neurologically normal older adults are "associated with reduced small vessel density, reduced myelin, and increased vacuolation." Overall, the study demonstrated that older adults with age-related changes in low frequency hearing are more likely to have hyperintensities that resemble the appearance and distribution of small vessel disease. The results of the study indicated that vascular disease is a factor that contributes to low frequency hearing loss. The study was conducted in older adults who did not exhibit any signs of cognitive impairment, and it was a relatively large imaging study that represented "the healthy older adult population for whom wide spread vessel disease may also affect vascular support to the cochlea and produce a decline in the stria vascularis that causes a drop in the endocochlear potential" [33].

Furthermore, with regards to white matter hyperintensities in patients with sudden hearing loss, a signal increase in cochlear lymph fluid on three dimensional fluid-attentuated inversion recovery(FLAIR) MRI sequences in patients with SSNHL has first been reported 10 years ago and additional reports have been reported about this finding since then. In one study, high signal on 3D FLAIR images has been reported to be detected in 95 out of 249 patients, and the degree of hearing loss was reported to be more severe in ears with high signal on 3D-FLAIR. In addition, the high signal on 3D-FLAIR was associated with a 2.88 times greater incidence of vertigo, and the "meta- analysis of the hearing recovery rate

showed the chance of recovery in the high signal group was significantly less than in the normal group." Furthermore, the signal increase was detected in two out of the six ears with severe SSNHL [34].

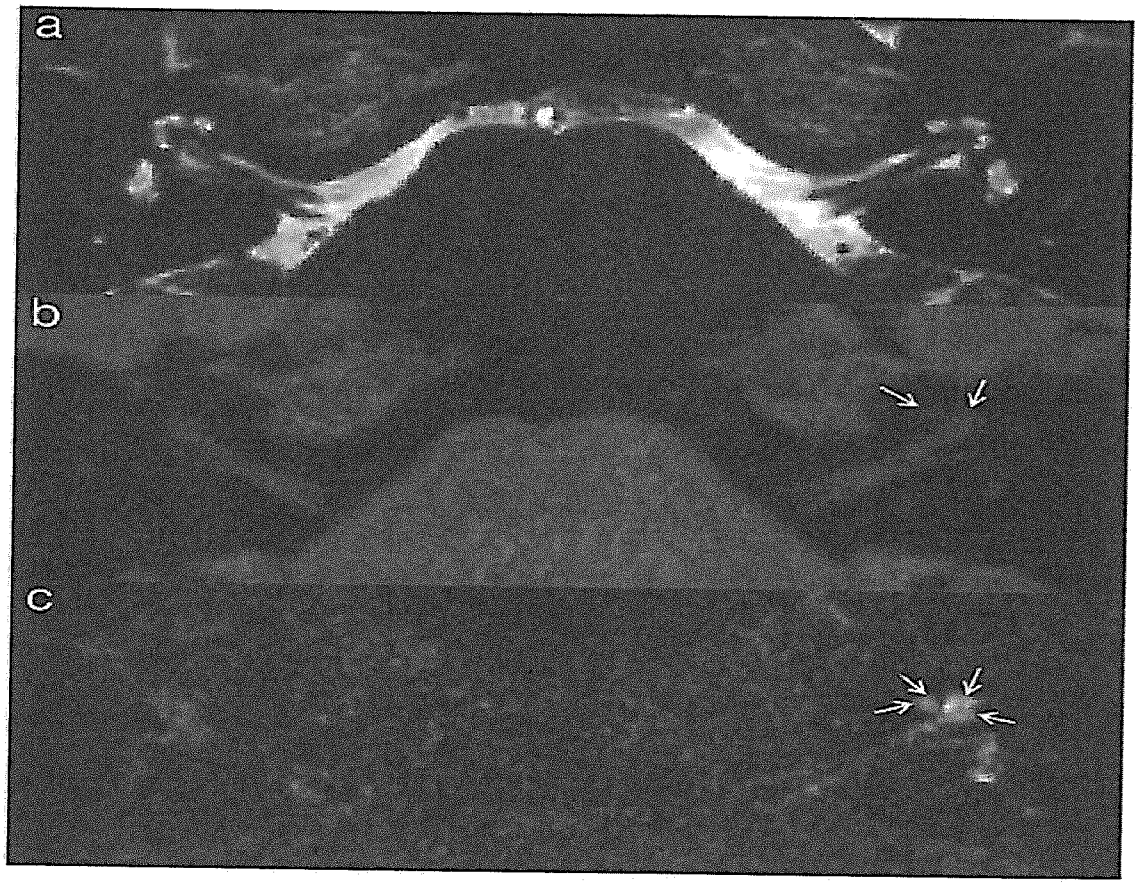

Figure 1.1. A 35-year old woman with severe SSNHL in her left ear. MR cisternography **(A)** regular T1-weighted contrast 3D-FLAIR **(B)** heavily T2- weighted 3D-FLAIR **(C)** The contrast-to-noise ratio between the affected and non-affected cochlea is 3.3 on T1-weighted and 5.8 on T2-weighted MRI. Signal increase is visually more prominent in T2 versus T1 weighted MRI. [34]

Additionally, since the etiology of SSNHL remains unclear, magnetic resonance imaging has been accepted as a sensitive imaging method to identify lesions in the cerebellopontine angle, internal auditory canal, and inner ear in patients with SSNHL. When researchers evaluated the MRI findings of the 291 patients with SSNHL and assessed the

frequency/characteristics of the detected abnormalities, they found that MRI abnormality was detected in 13 patients, which was considered a cause of SSNHL. The other 278 patients, who did not show MRI abnormality as a cause of SSNHL were diagnosed with idiopathic SSNHL, but some showed MRI findings such as mild chronic ischemic changes in bilateral cerebral white matter. Overall, the researchers found that 4.5% of patients with SSNHL exhibited abnormality on the internal auditory canal MRI, and the most common abnormality in the patients was vestibular schwannoma. Even though this study had its limitations because a definitive diagnosis by histopathologic examination could not be made in most patients, the study provided various examples of MRI abnormalities that are associated with SSNHL such as intralabyrinthine schwannoma, labyrinthine hemorrhage, IAC metastasis, and a ruptured dermoid cyst [35].

1.5 *Migraine Headaches and White Matter Hyperintensities*

Migraine is a chronic and debilitating condition that is characterized by recurrent headache attacks with symptoms related to the autonomic nervous system. Migraine is regarded as a risk factor that is associated with WMHs, which are frequently detected in the MRI scans of migraine patients. One population based study suggested that there was an increased risk of WMHs in migraine patients with higher attack frequencies, and the disease duration and attack frequency is associated with WMHs in migraine patients. Typically, WMHs associated with migraine tend to be punctate and mild. When the WMHs were investigated through T2-weighted and FLAIR MRI scans, 24 out of the 69 migraine patients were presented with WMHs (34.8%). Also, patients with WMHs were significantly older than the patients in the non-WMH group, and the disease duration was significantly higher in the WMH group than the non-WMH group. Furthermore, WMHs were significantly higher in the

frontal lobes (74.9%) and then followed by the parietal lobes (21.6%). The researchers noted that the WMHs in the migraine patients was generally mild and most lesions were <5mm, and the average number of WMHs(lesions) was generally small with a median number of 2.5. The accumulating evidence revealed that "migraine patients may have abnormal platelet activation, impaired endothelial function and hypercoagulability, which can potentially cause for the development of WMHs." Also, abnormal vascular conditions may favor the persistence or progression of migraine, and it is reasonable to speculate that WMHs can be correlated with unfavorable migraine prognosis. The results of the study demonstrated that the degree and frequency of the WMHs was positively correlated with unfavorable migraine prognosis. Overall, the study provided further evidence that WMHs can predict short-term unfavorable migraine prognosis and provided a new insight into the clinical significance of WMHs in migraine [36].

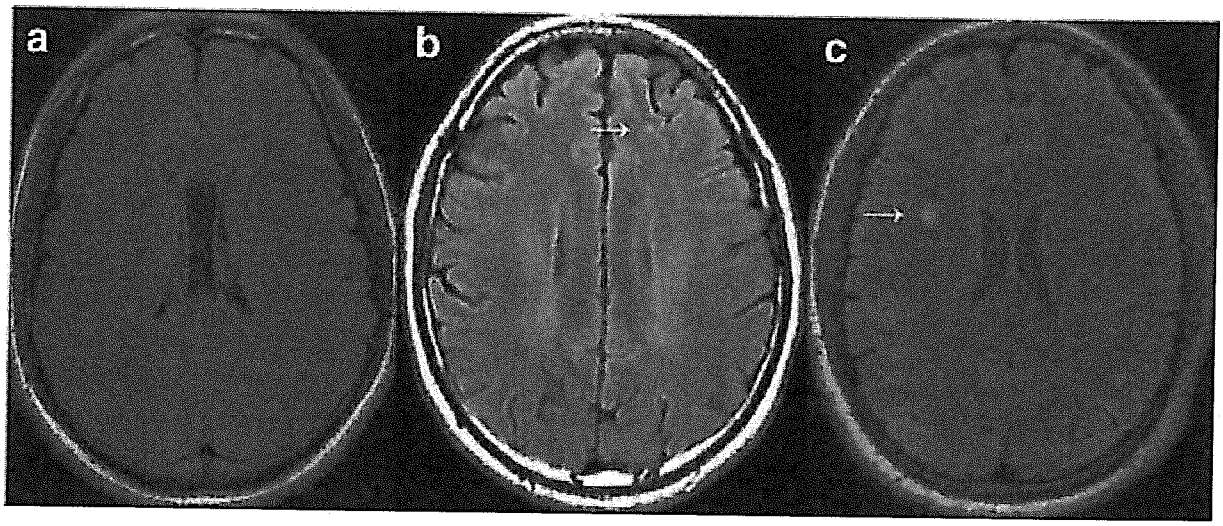

Figure 1.2. Representative axial FLAIR images of WMHs. **(A)** Normal brain structures without white matter hyperintensity **(B)** A puntuate hyperintense lesion (arrow) in the right frontal lobe **(C)** A confluent lesion (arrow) and some punctate lesions in the brain [36]

Furthermore, in another research study, scientists detected the prevalence of white matter hyperintensities in migraine patients in order to see its correlation with migraine severity, type, and duration. Ultimately, they found that WMHs were present in 43.1 % of migraine patients, and " age, presence of aura, nausea, disability during attack, resistance to treatment, and severity of headache and duration of migraine was considered a risk factor for development of WMHs." In the study, they found that the high grade of severity of migraine was associated with more WMHs, and this finding could be explained by "hemodynamic changes, neuronal activation or neurogenic inflammation, and disruption of blood brain barrier due to cortical spreading depression occurred in recurrent severe attacks of migraine" [37].

Some scientists believe that white matter hyperintensities are ischemic in origin, and they are associated with atherosclerotic disease risk factors, increased risk of ischemic stroke, and cognitive decline. The association of migraine with WMHs are consistent with the hypothesis that "recurring migraine headaches maybe associated with cerebral ischemia and that migraine-associated cerebral ischemia may be attack related." In order to determine whether men or women with migraine have a higher incidence of brain WMHs(lesions) 9 years after the initial MRI, whether migraine frequency was associated with progression of brain lesions and whether the progression of brain lesions was associated with cognitive decline, a group of scientists conducted a population based observational study with migraine and an age/sex-matched control group. The researchers found that after nine years, women with migraine had a higher incidence of deep white matter hyperintensities, but they did not have a significantly higher progression of other MRI measured brain

changes. In contrast, there was no association of migraine with progression of any MRI measured brain white matter hyperintensities in men [38].

Overall, the findings from the study suggested that sex differences seemed to play an important role because the progression of white matter hyperintensities was only found in women, which is in line with the results of a previous study that showed there is a higher risk of brain infarcts in women with migraine. In particular, the increase in the total deep white matter hyperintensity volume among women with migraine was related to an increased number of new lesions rather than an increase in the size of preexisting lesions. In the study, "participants in the migraine group had a higher incidence of 10 or more new lesions among 43 of 145 participants (30%) versus 5 of 57 in the control group (9%)." Additionally, among the women with migraine, the deep white matter hyperintensities were more diffusely distributed in the deep white matter than among controls. On the other hand, the progression of periventricular white matter hyperintensities did not differ between the migraine participants and controls, with no association of sex, aura status, or migraine frequency with progression [38].

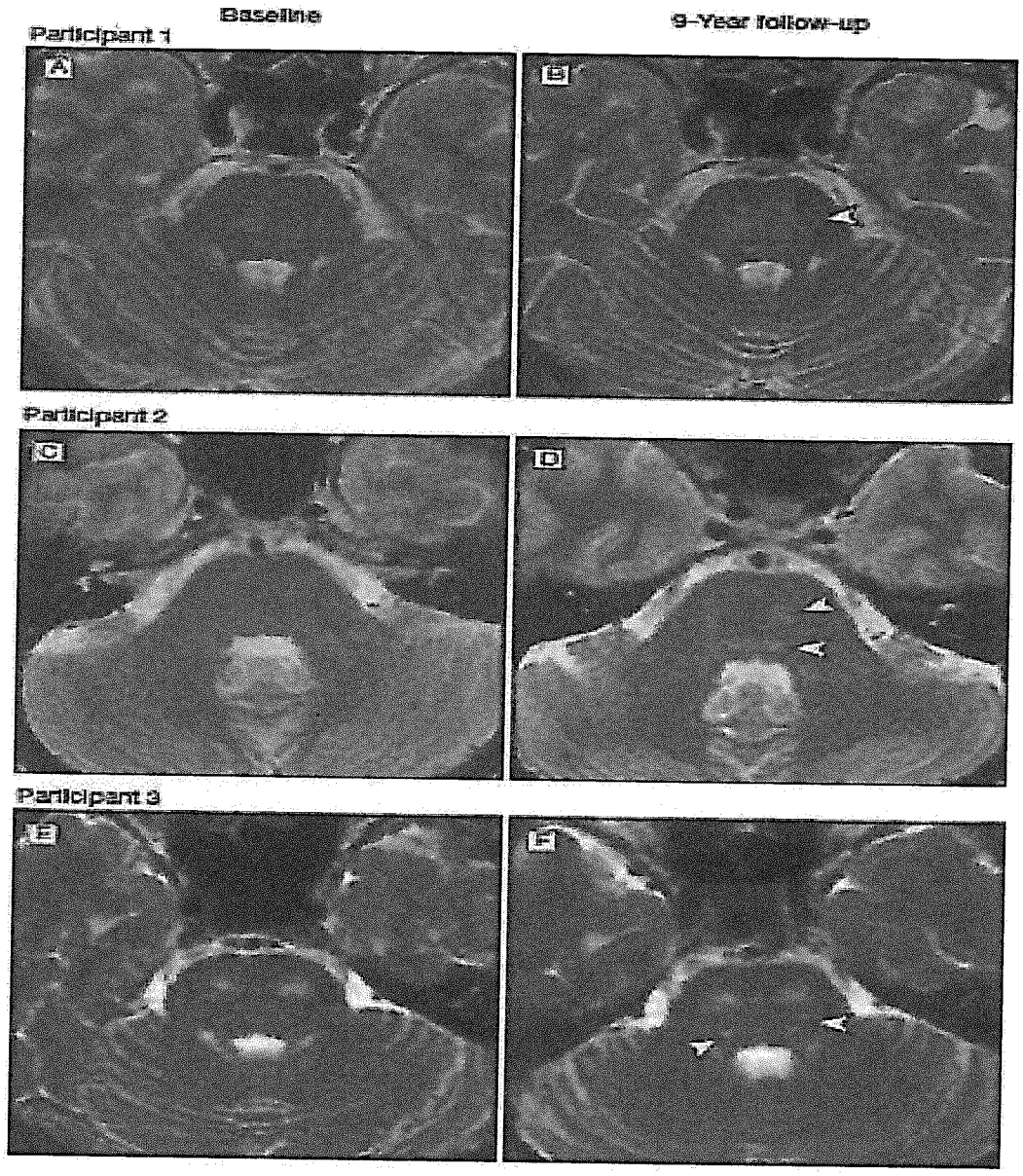

Figure 1.3. Brain Magnetic Resonance T2-Weighted MRI at Baseline and Follow-up From three Representative Participants Showing Progression of Infratentorial Hyperintensities
(1) Image B shows hyperintensity increased in size compared with baseline image A
(2) Image D shows new hyperintensities compared with baseline image C
(3) Image F shows additional hyperintensities compared with baseline image E [38]

On the other hand, in another study on migraine with aura and the risk of silent brain infarcts and white matter hyperintensities, scientists found that "the burden of deep WMHs, periventricular WMHs, and overall WMHs did not significantly differ in migraineurs

compared with non-migraineurs in case-control analyses, or in intra-pair analyses in twin pairs discordant for migraine with aura." Compared with control subjects, cases did not differ with regard to frequency of silent brain infarcts, periventricular white matter hyperintensity scores or deep white matter hyperintensity scores. However, cases had a slightly higher total white matter hyperintensity volume compared with controls and a similar difference was present in analyses restricted to twin pairs discordant for migraine with aura, but these differences did not reach statistical significance. Ultimately, the researchers found that there was not association between brain infarcts, white matter hyperintensities, and migraine with aura. However, some of the limitations of this study was that they could not draw conclusions on the sequence of events about whether the migraine onset predated the occurrence of WMHs, and the authors found no convincing effect of migraine on silent infarcts or WMHs. The study further concluded that the present results do not support the notion that female patients suffering from migraine have more silent infarcts and WMHs than females without migraines [39]. This conclusion contradicted the work of a previous published study that argued that women have an increase of white matter hyperintensities when suffering from migraines [38].

1.6 *Association of WMHs in Patients with Idiopathic SSNHL and Migraine Headaches*

In order to understand the etiological relationship between sudden sensorineural hearing loss and migraine headaches, we looked at the T2-weighted MRI scans of patients with these disorders and observed WMHs in each subgroup. Currently, no present research study has investigated WMHs in a unique patient population with both a migraine and sudden sensorineural hearing loss diagnosis. Existing studies that have investigated the

relationship between idiopathic SSNHL and migraine have been prospective cohort studies that have not studied the MRI scans of these illnesses simultaneously, For example, one epidemiological study explored the relationship between SSNHL and migraine at a tertiary referral center assessed 178 SSNHL cases from the Head and Neck Surgery Clinic patient database and found that SSNHL patients had a higher prevalence of migraine; however, patients with migraine had higher recovery rates, but the differences were not statistically significant. Of the sixty one idiopathic SSNHL patients, 55.74% were women and 39.34% had a migraine diagnosis [40]. Similarly, other population based studies have also demonstrated that migraine is associated with an increased risk of idiopathic SSNHL [23-25]. Therefore, we explored the relationship of these illnesses on a structural level by viewing white matter hyperintensities on T2-weighted MRI scans.

CHAPTER 2

METHODS

2.1 *Study Population*

The study included 150 normal young adult subjects (ages 22-35) from the Human Connectome Project (HCP). The data comprised of subjects from families with twins and non-twin siblings, using a protocol that includes structural magnetic resonance imaging at 3 Tesla. In all parts of the HCP, participants were scanned on the same equipment using the same protocol for every subject. All of the subject recruitment procedures and informed consent forms were approved by the Washington University in St. Louis Institutional Review Board (IRB), and all the experimental procedures were performed under the guidelines of the HCP, which adhered to the relevant IRB processes related to that project. The dataset analyzed for this study is currently available on the HCP page (https://www.humanconnectome.org/study/hcp-young-adult) [41].

Additionally, the study comprised of 150 subjects with sudden sensorineural hearing loss from the University of California, Irvine's Medical Center that were being treated in the Department of Otolaryngology. The T2-weighted MRI scans used from these subjects were collected on Epic Systems' IMPAX Database. Amongst these 150 sudden hearing loss patients, 25 of the patients also had a history of migraine. Therefore, the physician diagnosed these unique set of patients with migraine associated hearing loss. All patients were scanned on the same equipment using the same protocol. Furthermore, in order to remain consistent, solely the axial views on the T2-weighted images were used to conduct the analyses across all subjects.

2.2 *Assessment of Deep White Matter Hyperintensities and Periventricular Hyperintensities*

WMHs consist of deep white hyperintensities and periventricular hyperintensities. The assessment of WMHs was performed centrally by a single rater blinded to the clinical data of the study participants. The severity of the WMHs was rated visually on axial T2-weighted MRI scans using the Fazekas scale and Mirsen scale [42-43]. The Fazekas scale grades both deep white matter hyperintensities(absent, grade 0; punctuate, grade 1; early-confluent, grade 2; confluent, grade 3) and periventricular white matter hyperintensities (absent, grade 0; 'caps' or pencil thin lining, grade 1; smooth 'halo', grade 2; irregular periventricular signal extending into deep white matter, grade 3) on a rating scale. Grade 2 or 3 of the WMHs classified according to the Fazekas scale are progressive and likely malignant, whereas grades 0 to 1 are not progressive [44-45]. Infratentorial hyperintensities and basal ganglia were not rated as a part of this study. Additonally, the Mirsen scale also grades the number of deep white hyperintensities (absent, grade 0; one or two focal lesions, grade 1; three to five lesions, grade 2; more than five lesions, grade 3; confluent lesions, grade 4), and the periventricular white matter hyperintensities as simply absent or present. In the Mirsen scale, grades 2 to 4 likely represent malignancy and abnormality on the MRI scan [42]. Furthermore, all of the MRI scans were rated on the axial views.

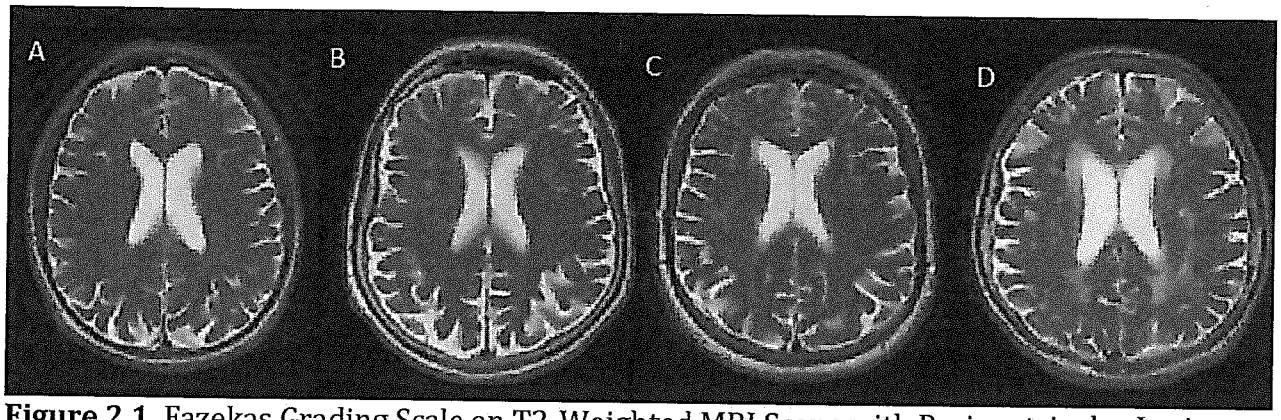

Figure 2.1. Fazekas Grading Scale on T2-Weighted MRI Scans with Periventricular Lesions **(A)** Grade 0, absent **(B)** Grade 1, 'caps' or pencil thin lining **(C)** Grade 2, smooth 'halo' **(D)** Grade 3, irregular periventricular signal extending into deep white matter

In the Mirsen scale, the periventricular hyperintensities are graded as present or absent; however, the deep white hyperintensities are graded based on number rather than confluency like the Fazekas scale. Therefore, a grade 1 on the Fazekas scale for deep white matter may be a grade of 2 on the Mirsen scale, if the number of hyperintensities is more than 5. These differences arise because the Mirsen scale focuses on the total count of hyperintensities (lesions). In contrast, the total count of lesions cannot be derived from the Fazekas scale, which is one of its limitations.

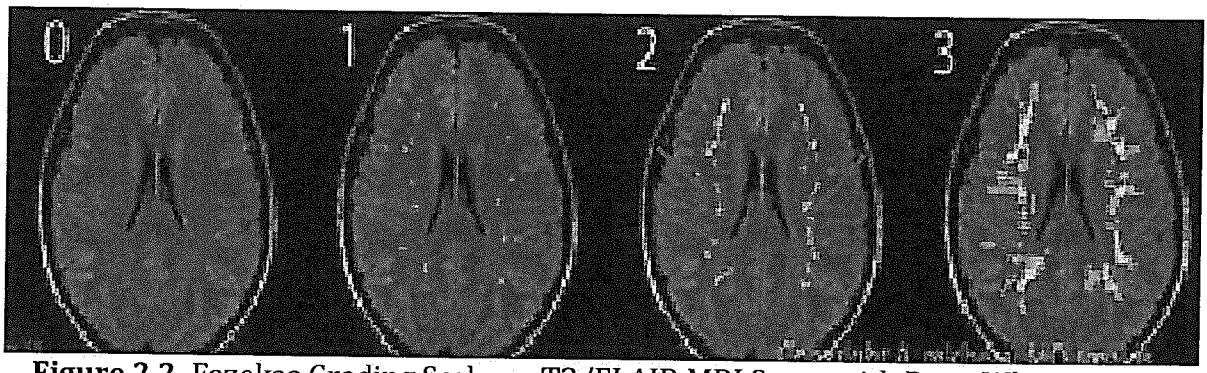

Figure 2.2. Fazekas Grading Scale on T2/FLAIR MRI Scans with Deep White Matter Lesions **(0)** Grade 0, absent **(1)** Grade 1, puntuate **(2)** Grade 2, early-confluent **(3)** Grade 3, confluent [46]

2.3 *Statistical Analyses*

For the statistical analysis, we used categorical variables as numbers and percentages and assessed the differences in the categorical variables according to the MRI scores using the chi-square test, and we described continuous variables as mean values ± standard errors, unless otherwise indicated. Based on their distribution, we estimated the differences in the continuous variables according to the MRI scores by student's t-test or the Wilcoxon's rank sum test. Lastly, we performed all statistical analyses using JMP software (v. 9.0; SAS Institute Inc) and STATA (v. 10; Stata Corporation). The differences at p-values of less than 0.05 were considered to be statistically significant [47].

CHAPTER 3

RESULTS

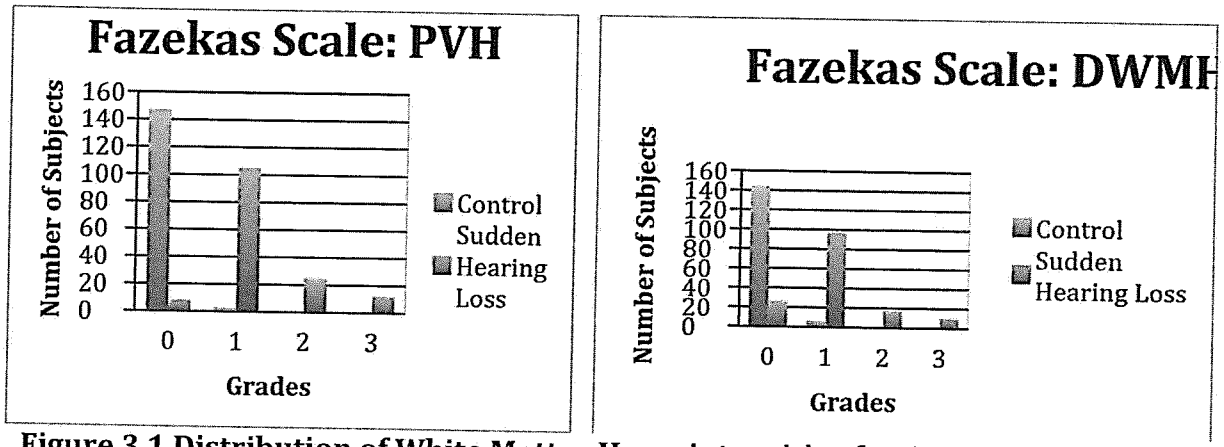

Figure 3.1 Distribution of White Matter Hyperintensities for Control and Sudden Hearing Loss Subjects Based on Fazekas Scale

FAZEKAS SCALE (%)	0	1	2	3
Deep White Matter Hyperintensities (DWMH)				
Controls (n=150)	144 (96%)	6 (4%)	0 (0%)	0 (0%)
Sudden Hearing Loss (n=150)	26 (17%)	97 (65%)	17 (11%)	10 (7%)
Migraine with Sudden Hearing Loss (n=25)	3 (12%)	19 (76%)	2 (8%)	1 (4%)
Periventricular White Matter Hyperintensities (PVH)				
Controls (n=150)	147 (98%)	3 (2%)	0 (0%)	0 (0%
Sudden Hearing Loss (n=150)	8 (5%)	105 (70%)	25 (17%)	12 (8%)
Migraine with Sudden Hearing Loss (n=25)	0 (0%)	19 (76%)	4 (16%)	2 (8%)

Table 3.1. Count of White Matter Hyperintensities Based on Fazekas Grading Scale

****Note:** The MRI study results are shown in Figure 3.1 and Table 3.1 for control (HCP) subjects, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis. The deep and periventricular white matter hyperintensities were rated in severity visually on axial T2- weighted images using the Fazekas scale.

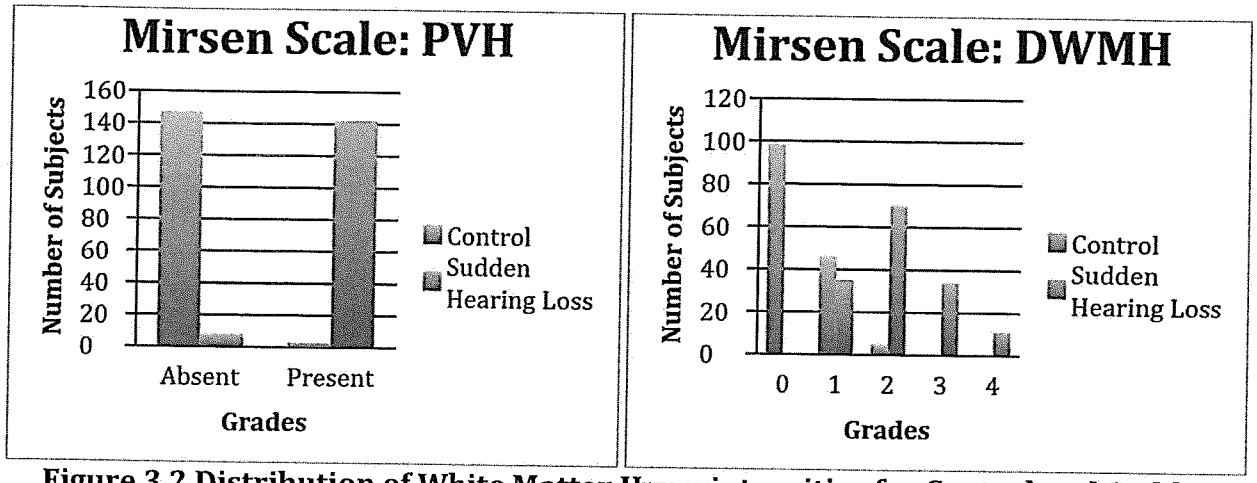

Figure 3.2 Distribution of White Matter Hyperintensities for Control and Sudden Hearing Loss Subjects Based on Mirsen Scale

MIRSEN SCALE (%)	0	1	2	3	4
Deep White Matter Hyperintensities (DWMH)					
Controls (n=150)	99 (66%)	46 (31%)	5 (3%)	0 (0%)	0 (0%)
Sudden Hearing Loss (n=150)	0 (0%)	35 (23%)	70 (47%)	34 (23%)	11 (7%)
Migraine with Sudden Hearing Loss (n=25)	0 (0%)	4 (16%)	15 (60%)	5 (2%)	1 (4%)
	Absent	**Present**			
Periventricular White Matter Hyperintensities (PVH)					
Controls (n=150)	147 (98%)	3 (2%)			
Sudden Hearing Loss (n=150)	8 (5%)	142 (95%)			
Migraine with Sudden Hearing Loss (n=25)	0 (0%)	25 (100%)			

Table 3.2. Count of White Matter Hyperintensities Based on Fazekas Grading Scale

****Note:** The MRI study results are shown in Figure 3.2 and Table 3.2 for control (HCP) subjects, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis. The deep and periventricular white matter hyperintensities were rated in severity visually on axial T2- weighted images using the Mirsen scale. Unlike the Fazekas scale, the Mirsen scale rates periventricular hyperintensities as either absent or present. Additionally, the Mirsen scale, for DWMHs, focuses on the number of punctuate lesions, which is contains a slightly wider scale.

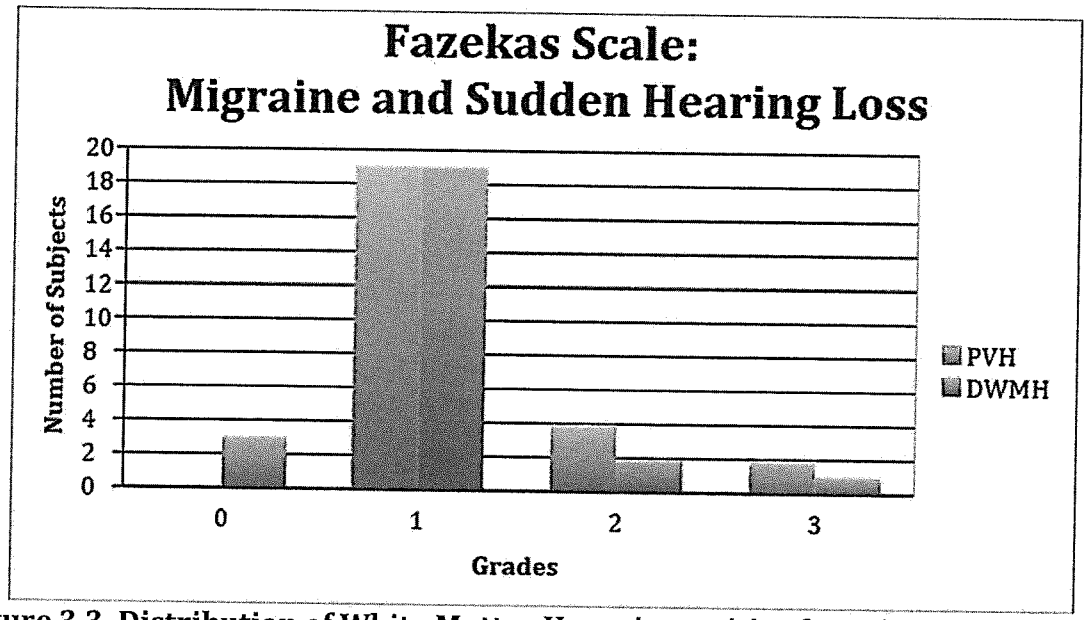

Figure 3.3. Distribution of White Matter Hyperintensities for Subjects with Both Migraine and Sudden Hearing Loss Diagnosis Based on Fazekas Scale

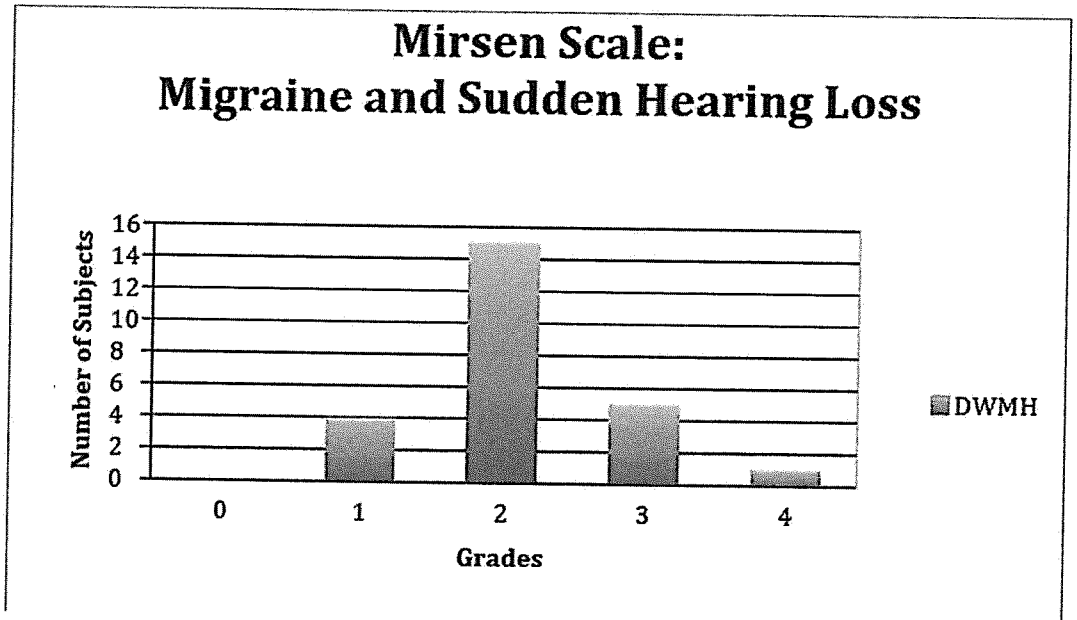

Figure 3.4 Distribution of Deep White Matter Hyperintensities for Subjects with Both Migraine and Sudden Hearing Loss Diagnosis Based on Mirsen Scale

****Note:** The periventricular white matter hyperintensities (PVH) are not displayed on the Mirsen Scale graph because they are denoted as either absent or present in the grading scale, and all 25 subjects with the Migraine and Sudden Hearing Loss diagnosis had PVHs on their MRI scans.

Mean WMH Scores	Mean Fazekas Score (SD) ± SE	Mean Mirsen Score (SD) ± SE
Periventricular White Matter Hyperintensities (PVH)		
Controls (n=150)	0.02 (0.14) ± 0.01	N/A
Sudden Hearing Loss (n=150)	1.27 (0.68) ± 0.06	N/A
Migraine with Sudden Hearing Loss (n=25)	1.32 (0.63) ± 0.07	N/A
Deep White Matter Hyperintensities (DWMH)		
Controls (n=150)	0.04 (0.20) ± 0.02*	0.37 (0.55) ± 0.04*
Sudden Hearing Loss (n=150)	1.07 (0.74) ± 0.06*	2.14 (0.86) ± 0.07*
Migraine with Sudden Hearing Loss (n=25)	1.04 (0.61) ± 0.12*	2.12 (0.73) ± 0.15*

Abbreviations: SD = Standard Deviation; SE = Standard Error ;
*** Statistical significance was expressed by p value < 0.05**

Table 3.3. Mean Fazekas and Mirsen PVH and DWMH Grading Scores

CHAPTER 4

DISCUSSION

4.1 *WMHs in Control and Sudden Hearing Loss Subjects*

As hypothesized, there were a significantly larger number of DWMHs and PVHs in sudden hearing loss subjects versus the control subjects. In the Fazekas scale, 96% of the control subjects had a grade of 0 for DWMHs, and 98% of them had a grade of 0 for PVHs. Therefore, the vast majority had an absence of lesions. Confounding variables, such as age, were controlled for because all control subjects (healthy adults) were between the ages of 22-35. Typically, WMHs are often observed on T2-weighted images of the brain in elderly subjects, and the prevalence of these lesions rises steadily with increasing age [48]. Additionally, based on the Fazekas scale, the sudden hearing loss subjects had substantial amounts of DWMHs and PVHs. For DWMHs, 11% had grade 2 and 7% had grade 3, which represents progressive or malignant lesions. Similarly, for PVHs in the sudden hearing loss subjects, 17% had grade 2 and 8% had grade 3 ratings, which illustrates that a smooth halo or irregular periventricular signal is extending into deep white matter.

Although the Mirsen scale showed different results, the trends seen on the Fazekas scale was also seen on the Mirsen scale. The majority of control subjects had an absence of DWMHs and PVHs, at 66% and 98% respectively. However, 31% of controls had a grade 1 for DWMHs because the Mirsen scale grades one or two punctuate lesions with a grade, even though these particular hyperintensities are not significant enough to be labeled malignant. Furthermore, for sudden hearing loss subjects, 95% had a presence of PVHs and most of the subjects contained DWMHs. Of these sudden hearing loss subjects, 47% had grade 2, 23%

had grade 3, and 7% had grade 4 DWMHs. Therefore, a total 77% had a malignant number of hyperintensities.

Overall, our results were consistent with previous studies that studied WMHs in sudden hearing loss patients. For example, when researchers previously evaluated MRI findings of 291 patients with SSNHL and assessed abnormalities, they found that MRI abnormality was detected in 13 patients, and the other 278 patients showed MRI findings such as mild ischemic changes in bilateral cerebral white matter [35]. Although our work focuses on deep and periventricular white matter, our results confirm the abnormalities are frequently seen on MRI scans of patients.

4.2 *WMHs in Subjects with Both Sudden Hearing Loss and Migraine Headaches*

In order to look at the association of sudden hearing loss and migraine headaches, we looked at WMHs in subjects with both of these disorders. Specifically, 25 subjects in our data from the University of California, Irvine's Department of Otolaryngology had both of these diagnoses simultaneously. These unique subset of patients had a history of migraine and were currently suffering from sudden hearing loss. Based on the Fazekas scale, we found that 76% had grade 1, 8% had grade 2, and 4% had grade 3 DWMHs. Similarly, 76% had grade 1, 16% had grade 2, and 8% had grade 3 PVHs. Therefore, compared to the control subjects, many more of these subjects contained hyperintensities on their MRI that would be considered progressive or malignant. Similarly, these trends were seen on the Mirsen scale because 100% of these subjects had PVHs, and the majority had grade 2 (60%) or grade 3 (2%) rating for DWMHs.

Our results are consistent with previous findings about the existence of WMHs in patients with migraine and those suffering from sudden hearing loss. For instance, one study about migraine with aura and the risk of brain infarcts found that patients with migraine had a slightly higher total white matter hyperintensity volume compared with controls [39]. Furthermore, in another study regarding the incidence of WMHs in migraine subjects found that after nine years, women with migraine had a higher incidence of deep white matter hyperintensities [38]. Overall, our results are consistent with previous work about WMHs in migraine subjects and sudden hearing loss subjects independently. However, our study goes further to see whether sudden hearing loss patients with a history of migraine consistently contain these structural abnormalities on their MRI scans.

The WMHs seen on the T2- weighted MRI scans of the 25 subjects with both migraine and sudden hearing loss illustrates the association of hyperintensities on subjects with these illnesses. WMHs are seen all over the white matter of the subjects and are not restricted to one region. By viewing these lesions on the MRI scans, our work suggests an associated link between the two illnesses. Previous population based studies have shown tremendous evidence about the association of migraine and sudden hearing loss [23-25]. Therefore, our study goes one step further in demonstrating the link on a structural level using magnetic resonance imaging.

4.4 *Limitations*

Nonetheless, our present study has a few limitations. For example, our dataset contained a relatively small number of patients with both sudden hearing loss and migraine headaches. Furthermore, the age of the patients with sudden hearing loss and those with migraine headaches should be controlled in the design of the study. Thus, future work should

focus on investigating the implication of WMHs among a relatively young patient population. Additionally, the heterogeneity of the patient cohort such as "migraine with and without aura, episodic migraine and chronic migraine should be improved" because different types of migraine may have different effects on the prognosis of sudden hearing loss. Also, future work should employ more stable parameters to assess disease burden in order to confirm the clinical significance of WMHs, since we could not effectively investigate other WMH associated risk factors, including "hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, hyperuricemia, hypercoagulability, heart diseases, kidney diseases, inflammation and autoimmune diseases" [26]. Therefore, future studies should be controlled for the confounding variables mentioned above.

4.3 *Future Directions*

Overall, future work should focus on controlling confounding variables in the patient population. Additionally, a larger sample set should be assessed for WMHs in a group of sudden hearing loss and migraine subjects. Another limitation of this study was that we could not draw conclusions about the sequence of events about whether migraine onset predated the occurrence of WMHs in the sudden hearing loss subjects. Therefore, in order to see a causal association between migraine and sudden hearing loss using MRI scans, we would need to know the sequence of events regarding the onset of migraine headaches, the development of WMHs, and the beginning of sudden hearing loss. The typical sequence of symptoms of patients is migraine headaches followed by hearing loss followed by vertigo [23].

CHAPTER 5

CONCLUSIONS

Although sudden hearing loss is most often attributed to infectious, vascular, traumatic, and autoimmune causes, another potential link to sudden hearing loss is migraine headaches. In order to further investigate the association of migraine in cases of sudden hearing loss, we looked at T2-weighted MRI sequences of normal healthy adults, sudden hearing loss patients, and sudden hearing loss patients with a migraine diagnosis. Specifically, we looked at white matter hyperintensities on T2-weighted MRI scans of all the respective subjects. WMH are clinically important biomarkers; thus, when physicians are making clinical diagnoses, which likely represent a mixture of pathologies, they ought to focus on intermediary markers of brain damage such as WMHs.

In order to look at the association of sudden hearing loss and migraine headaches, we looked at WMHs in subjects with both of these disorders. These unique subset of patients had a history of migraine and were currently suffering from sudden hearing loss. The majority of these subjects had progressive or malignant WMHs on their T2-weighted MRI scans. Compared to the control subjects, many more of the sudden hearing loss/migraine subjects contained hyperintensities on their MRI that would be considered progressive or malignant. Our results are consistent with previous findings about the existence of WMHs in patients with migraine and those suffering from sudden hearing loss. However, our study goes further to see whether sudden hearing loss patients with a history of migraine consistently contain these structural abnormalities on their MRI scans.

By viewing WMHs on the MRI scans, our work suggests an associated link between the two illnesses. Previous population based studies have shown tremendous evidence

about the association of migraine and sudden hearing loss [23-25]. Therefore, our work is consistent with previous findings but illustrates the link between migraine and sudden hearing loss on a structural level using magnetic resonance imaging. Overall, by finding structural similarities on the MRI scans of these respective subjects, our work suggests a possible link amongst the two illnesses, which would helps in the development of better treatment options for patients with this debilitating disorder.

REFERENCES

[1] Rauch, S.D., *Idiopathic sudden sensorineural hearing loss.* N Engl J Med, 2008. 359(8): p. 833-840.

[2] Kuhn, M., et al., *Sudden Sensorineural Hearing Loss: A Review of Diagnosis, Treatment, and Prognosis.* Trends Amplif, 2011. 15(3): p. 91-105.

[3] Uri, N., et al., *Acyclovir in the treatment of idiopathic sudden sensorineural hearing loss.* Otolaryngol Head Neck Surg, 2003, 128(4): p. 544-549.

[4] Stokroos, R.J., et al. *Antiviral treatment of Idiopathic Sudden Sensorineural Hearing Loss: A prospective, randomized, double-blind clinical trial.* Acta Otolaryngol, 1998, 118(4): p. 488-495.

[5] Hultcrantz, E., et al. *Sympathetic effects on cochlear blood flow at different blood pressure levels.* Inserm, 1977, 68: p. 271-278.

[6] Scheibe, F., et al. *Effects of experimental cochlear thrombosis on oxygenation and auditory function of the inner ear.* Eur Arch Otorhinolaryngol, 1997, 254(2): p.91-94.

[7] Hultcrantz, E., et al. *Sudden deafness: a retrospective evaluation of dextran therapy.* ORL J Otorhinolaryngol Relat Spec, 1994, 56(3): p. 137-142.

[8] Topuz, E., et al. *Should hyperbaric oxygen be added to treatment in idiopathic sudden sensorineural hearing loss?* Eur Arch Otorhinolaryngol, 2004, 261(7): p.393-396.

[9] De Oliveira Penido, N., et al. *Clinical, etiological and progression factors of hearing in sudden deafness,* Braz J Otorhinolaryngol., 2005, 71(5): p.633-638.

[10] Probst, R., et al. *A randomized, double-blind, placebo-controlled study of dextran/pentoxifylline medication in acute acoustic trauma and sudden hearing loss,* Acta Otolaryngol, 1992, 112(3): p. 435-443.

[11] Kronenberg, J., et al. *Vasoactive therapy versus placebo in the treatment of sudden hearing loss: A double-blind clinical study,* Laryngoscope, 1992, 102(1): p. 65-68.

[12] Vasama, J.P., et al. *Idiopathic sudden sensorineural hearing loss: Temporal bone histopathologic study,* Ann Otol Rhinol Laryngol, 2000, 109(6): p. 527-532.

[13] Schuknecht, H.F., et al. *The pathology of idiopathic sudden sensorineural hearing loss,* Arch Otorhinolaryngol, 1986, 243 (1): p. 1-15.

[14] Merchant, S.N., et al. *Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss,* Otol Neurotol, 2005, 26 (2): p. 151-160.

[15] Cole, R.R. et al. *Sudden hearing loss: an update,* An J Otol, 1988, 9(3): p. 211-215.

[16] Cadoni, G., et al. *Sudden hearing loss in a patient hepatitis C virus (HCV) positive on therapy with alpha-interferon: a possible autoimmune-microvascular pathogenesis,* J Laryngol Otol, 1998, 112(10): p. 962-963.

[17] Yoshida, Y., et al. *Immunological and virological study of sudden deafness,* Auris Nasus Larynx, 1996, 23: p. 63-68.

[18] Rossini, B.A., et al. *Sudden Sensorineural Hearing Loss and Autoimmune Systemic Diseases,* Int Arch Otorhinolaryngol, 2017, 21(3): p. 213-223.

[19] Shimazaki, T., et al. *Localization of glucocorticoid receptors in the murine inner ear,* Ann Otol Rhinol Laryngol, 2002, 111(12): p. 1133-1138.

[20] Kanzaki , J., et al. *Evaluation of hearing recovery and efficacy of steroid treatment in sudden deafness,* Acta Otolaryngol Suppl, 1988, 106(456): p. 31-36.

[21] Kurokawa, T., et al. *Four cases of idiopathic sudden sensorineural hearing loss*, Pract Otolog, 1998, 91(3): p. 221-225.
[22] Jeyakumar, A., et al. *Treatment of idiopathic sudden sensorineural hearing loss*, Acta Otolaryngol, 2006, 126(7): p. 708-713.
[23] Viirre, E.S., et al. *Migraine as a Cause of Sudden Hearing Loss*, Headache, 1996, 36(1): p. 24-8.
[24] Cha, Yoon-Hee., et al. *Migraine a risk factor for SSNHL*, Cephalalgia, 2012, 33(2): p. 77-79.
[25] Kim, So Young, et al., *Migraine increases the proportion of sudden sensorineural hearing loss: A longitudinal follow-up study*, Auris Nasus Larynx, 2018, S0385-8146(18)30584-4.
[26] Wardlaw, Joanna, et al., *What are White Matter Hyperintensities Made of? Relevance to Vascular Cognitive Impairment*, J Am Heart Assoc, 2015, 4:e001140.
[27] Pickles, J.O., *An introduction to the physiology of hearing*, 2nd ed. Academic press, London;, 1988.
[28] Kirikae, I., et al. *The capillary in the human cochlea*, Acta Otolaryngol, 1969, 67(1):1-8.
[29] Roeser, R.J., et al. *Audiology diagnosis*, 1st ed. Thieme Medical Publishers, New York;, 2000.
[30] Haller, Sven., et al. *Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study*, Acta Neuropathol Commun, 2013, 1(14): 10.1186/2051-5960-1-14.
[31] Kim, T.W., et al. *White matter hyperintensities and cognitive dysfunction in patients with infratentorial stroke*, Ann Rehabil Med, 2014, 38(5): 620-627.
[32] Cho, Jiwon., et al. *Sudden sensorineural hearing loss associated with inner ear lesions detected by magnetic resonance imaging*, PLoS One, 2017, 12(10): e0186038.
[33] Eckert, M., et al. *White matter hyperintensities predict low frequency hearing in older adults*, J Assoc Res Otolaryngol, 2013, 14(3): 425-433.
[34] Naganawa, Shinji, et al., *Heavily T2-weighted 3D-flair improves the detection of cochlear lymph fluid signal abnormalities in patients with sudden sensorineural hearing loss.* Magn Reson Med Sci, 2016; 15(2): 203-211.
[35] Jeong, Kyung-Hwa., et al., *Abnormal magnetic resonance imaging findings in patients with sudden sensorineural hearing loss, Medicine (Baltimore)*, 2016, 95(17): e3557.
[36] Xie, Hui, et al., *Association of white matter hyperintensities with migraine features and prognosis*, BMC Neurol, 2018; 18(93): 10.1185/s12883-018-1096-2.
[37] Negm, Mohamed., et al. *Relation between migraine pattern and white matter hyperintensities in brain magnetic resonance imaging*, Egypt J Neurol Psychiatr Neurosurg, 2018; 54(1): 24.
[38] Palm-Meinders, Inge., et al. *Structural brain changes in migraine*, JAMA, 2013, 308(18): 1889-1897.
[39] Gaist, David., et al. *Migraine with aura and risk of silent brain infarcts and white matter hyperintensities: an MRI study*, Brain, 2016, 139(7): 2015-2023.
[40] Arslan, Yildiz., et al. *The etiological relationship between migraine and sudden hearing loss, Otology & Neurotology*, 2017, 38(10):1411-1414.
[41]Glasser, MF., *The Human Connectome Project's neuroimaging approach*, Nature Neuroscience, 2016; 19: 1175-1187.
[42] Fazekas, F., et al. *MR signal abnormalities at 1.5T in Alzhiemer's dementia and normal aging*, AJR Am J Roantgenol. 1987; 149:351-356.

[43] Mirsen. Thomas., et al., *Clinical correlates of white-matter changes on magnetic resonance imaging scans of the brain*, Arch Neurol, 1991; 48: 1015-1021.
[44]Schmidt, R., et al., *Progression of cerebral white matter lesions; 6-year results of the Austrian stroke prevention study*, Lancet, 2003; 361:2046-2048.
[45]Dufail, C., et al., *Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the progress (perindopril protection against recurrent stroke study) magnetic resonance imaging substudy*, Circulation, 2005; 112: 1644-1650.
[46] Heart Mind Journal online. Heart Mind Institute [accessed 2019 Jan 30] http://www.heartmindjournal.org/viewimage.asp?img=HeartMind_2017_1_1_22_206966_f1.jpg; Heart Mind Journal, 2019.
[47] Takami, Takeshi., et al., *Major risk factors for the appearance of white-matter lesons on MRI in hyperintensive patients with controlled blood pressure*, Vascular Health and Risk Management, 2012; 8: 169-176.
[48] Split, Aart., et al., *Age-related changes in normal-appearing brain tissue and white matter hyperintensities: more of the same or something else*, American Journal of Neuroradiology, 2005; 26(4): 725-729.