Evidence-Based Prediction of Cochlear Implantation Outcomes

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“Not being able to see separates people from things;

not being able to hear separates people from people”

Immanuel Kant (1724-1804)

Abstract

Objectives The goal of this thesis is to critically review and synthesize evidence-based findings regarding the prediction of cochlear implantation outcomes in certain patient populations. This thesis will aim to clarify questions regarding stapedotomy versus cochlear implantation for advanced otosclerosis, to yield new knowledge on the association of GJB2 mutation status with the outcomes of pediatric cochlear implantation, and to shed new light on auditory streaming in cochlear implantation recipients.

Methods In the first part of this thesis, we systematically analyzed and synthesized the existing evidence in order to assess the outcomes of the two treatment methods for advanced otosclerosis: cochlear implantation and stapedotomy. We also synthesized the existing evidence in order to assess the predictive value of the GJB2 mutation status on the outcomes of pediatric cochlear implantation. In the second part, we investigated whether cochlear implantation users are capable of perceiving auditory stream segregation and how they differ from normal hearing listeners. To do so, 26 cochlear implantation recipients and 12 normal hearing controls were tested for their responses to a series of stimulus consisting of different sound sequences. At the end of each block, participants were asked to report how many different pitches they could detect from the sequence and whether these tones were perceived as originating from a single or from two distinct sound sources. From the participants' responses, the proportions of perception as either one-stream or two-stream were calculated for each condition. In addition, whether factors including age, level of education and formal music education have any impact on streaming capability was analyzed.

Results (1) Cochlear implantation leads to a statistically greater and consistent improvement in speech recognition scores when compared to stapedotomy. Stapedotomy is not universally effective; however, it yields results comparable to cochlear implantation in a substantial amount of patients. (2) GJB2-related deafness was associated with significantly better cochlear implantation outcomes when compared to acquired hearing loss due to environmental etiologies. However, if the control groups were matched carefully with respect to the factors that are known to affect language development, such as age at implantation, etiology of hearing loss and absence of co-morbidities, there is no significant advantage of harboring a GJB2 mutation over hearing

loss from unknown etiologies or other types of genetic deafness with no additional disabilities. (3) When the frequency separation between the A and B harmonic complexes is small, cochlear implantation users showed significantly less favorable streaming abilities than normal hearing listeners. However, with the increase of the frequency separation between the A and B tone, CI users showed the same steady increase of the two-stream percept as normal hearing controls. This finding provides evidence that, most CI users show the same stream segregation as normal-hearing listeners.

Conclusions (1) For patients of advanced otosclerosis, CI leads to statistically greater and consistent speech discrimination scores than stapedotomy. (2) GJB2-related deafness associates with significantly better CI outcomes when compared to an acquired hearing loss due to environmental etiologies. However, if the factors that affect language development are controlled, there is no significant advantage of harboring a GJB2 mutation over a hearing loss of unknown etiologies or other types of genetic deafness with an absence of other disabilities. (3) Most CI users show stream segregation just as normal-hearing listeners do. The quality of streaming formation is not altered when the auditory input is provided via a CI.

Résumé

Objectifs : L'objectif de cette thèse consiste à évaluer de façon critique et à synthétiser les conclusions fondées sur les données probantes concernant la prévision des résultats d'un implant cochléaire chez certaines populations de patients. Cette thèse visera à clarifier les questions relatives à la stapédotomie par opposition aux implants cochléaires pour l'otosclérose avancée, afin d'acquérir de nouvelles connaissances sur l'association de la mutation GJB2 avec les résultats produits par un implant cochléaire pédiatrique et pour apporter un nouvel éclairage sur le phénomème de flux auditif chez les personnes avec implant cochléaire.

Méthodologie Dans la première partie de cette thèse, nous analysons et synthétisons systématiquement les données existantes afin d'évaluer l'issue de deux méthodes de traitement pour l'otosclérose avancée : l'implant cochléaire et stapédotomie. Nous synthétisons également les données existantes dans le but d'évaluer la valeur prédictive de la mutation GJB2 par rapport aux conséquences d'un implant cochléaire pédiatrique. Dans la deuxième partie, nous cherchons à savoir si les utilisateurs d'implants cochléaires sont capables de percevoir la ségrégation de flux auditifs et comment ils se différencient des personnes ayant une audition normale. Pour y parvenir, 26 personnes avec implant cochléaire et 12 témoins avec ouïe normale ont été testés par rapport à une série de stimulus consistant en différentes séquences de son. À la fin de chaque bloc, les participants ont été invités à mentionner le nombre de tons qu'ils pouvaient distinguer dans une séquence et s'ils percevaient ces tons comme provenant d'une seule ou deux sources distinctes de son. À partir des réponses des participants, la proportion de perception d'un flux ou de deux flux a été calculée pour chaque condition. En plus, la question de savoir si des facteurs tels que l'âge, le niveau d'éducation et l'éducation musicale en milieu scolaire avaient un impact sur la capacité de flux a été analysée.

Résultats (1) Les implants cochléaires mènent à une amélioration significative de la reconnaissance de parole en comparaison à la stapédotomie. La stapédotomie n'est pas efficace universellement; toutefois, elle produit des résultats comparables aux implants cochléaires chez une proportion substantielle de patients. (2) La surdité reliée à la mutation GJB2 est reliée à des résultats significativement meilleurs dans les cas d'implant cochléaire comparativement à la perte d'ouïe liée à une étiologie environnementale. Toutefois, si les groupes de contrôle étaient

jumelés en prêtant une attention particulière aux facteurs étant connus comme affectant le développement du langage, tels que l'âge de l'implantation, l'étiologie de la perte d'ouïe et l'absence de comorbité, il n'existe alors aucun avantage important à détenir une mutation GJB2 plutôt qu'une perte d'ouïe reliée à une étiologie inconnue ou d'autres types de surdité génétique sans handicap additionnel. (3) Lorsque la fréquence de séparation entre les harmoniques complexes A et B est petite, les utilisateurs d'implant cochléaire montraient des capacités de flux significativement moins favorables que les personnes ayant une ouïe normale. Toutefois, en augmentant la fréquence de séparation entre les tons A et B, les utilisateurs d'implants ont montré la même augmentation stable de la perception des deux flux que les personnes ayant une audition normale. Cette découverte démontre que la plupart des utilisateurs d'implant cochléaire possèdent la même ségrégation de flux que les personnes à audition normale.

Conclusions : (1) Pour les patients atteints d'une otosclérose avancée, les implants cochléaires mènent à des scores en discrimination auditive statistiquement plus grands et cohérents que la stapédotomie. (2) La surdité reliée à la mutation GJB2 est reliée à des résultats significativement meilleurs dans les cas d'implant cochléaire comparativement à la perte d'ouïe liée à une étiologie environnementale. Toutefois, si les facteurs affectant le développement du langage sont contrôlés, il n'existe aucun avantage significatif à porter une mutation GJB2 plutôt qu'une perte d'audition liée à une étiologie inconnue ou d'autres types de surdité génétique avec une absence d'autres handicaps. (3) La plupart des utilisateurs d'implant cochléaire montrent une ségrégation semblable à celle des personnes ayant une audition normale. La qualité de la formation des flux n'est pas altérée lorsque l'audition est transmise grâce à un implant cochléaire.

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List of Abbreviations

THFC: The Hearing Foundation of Canada
CI: Cochlear implantation
GJB2: Gap Junction B-2
FDA: Food and Drug Administration
IAC: Internal Auditory Canal
BCNC: bony cochlear nerve canal
ABI: auditory brainstem implant
EHDI: Early Hearing Detection and Intervention
ASHA: American Speech-Language-Hearing Association
SNHL: Sensorineural Hearing Loss
FAO: Far Advanced Otosclerosis
AC: Air Conduction
BC: Bone Conduction
ABG: Air Bone Gap
WRS: Word Recognition Scores
SRS: Sentence Recognition Scores
PTA: Pure Tone Audiometry
CID: Central Institute for the Deaf sentence test
HINT: Hearing in Noise Test
IT–MAIS: Infant Toddler Meaningful Auditory Integration Scale
CAP: Categorized Auditory Performance
SIR: Speech Intelligibility Rating
CMV: Cytomegalo virus
ADHD: Attention Deficit Hyperactivity Disorder
LE: Level of Evidence
CRIR: Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal
ISI: Interstimulus interval
ST: Streaming threshold
AMT: Amplitude modulation threshold
NH: Normal Hearing

Dedication

This thesis is dedicated with love to my wife, Minawar and to my sons, Yarkin and Yadikar. Your unwavering encouragement, love, and support are what helped me through my time in McGill University as a graduate student. I will never be able to thank you enough for looking after the kids alone, far away from me.

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Preface

Contributions of Authors

Dr. Yasin Abdurehim was responsible for the literature review in its entirety. For the manuscript1 (Stapedotomy versus Cochlear Implantation for Advanced Otosclerosis) and manuscript2 (Predictive Value of GJB2 Mutation Status for Hearing Outcomes in Pediatric Cochlear Implantation), Dr. Abdurehim was responsible for the concept, design, data collection, analysis of results, and drafting of the initial manuscripts. Dr. Anthony Zeitouni and Dr. Alexandre Lehmann provided supervision, critical review & editing. For manuscript3 (Auditory Streaming in Cochlear Implant Recipients), Dr. Lehmann and Dr. Zeitouni contributed to the experiment designing, guidance, result interpretation and final approval. Dr. Abdurehim was responsible for data collection, statistical analysis, result interpretation and drafting of the initial manuscripts.

Claims of Originality

(1) Compared to stapedotomy, CI leads to a statistically greater and consistent speech discrimination scores in patients of advanced otosclerosis. For cases of unsuccessful stapedotomy, CI still works well and the results obtained by a salvage CI are as good as those of a primary CI. (2) GJB2-related deafness is associated with significantly better CI outcomes when compared to hearing loss of environmental etiologies. However, if the factors that affect language development are accounted for and with the absence of other disabilities, there is no significant advantage of carrying a GJB2 mutation on CI outcomes. (3) Most CI users show the same stream-segregation capability as normal-hearing listeners.

CHAPTER ONE: Introduction

1.1 Thesis Rationale

According to The Hearing Foundation of Canada (THFC), more than 2,000 children are born with a hearing loss in Canada each year, making it one of the nation's most common birth defects[1]. Globally, approximately 1 to 6 in every 1,000 children is born with severe to profound sensorineural hearing loss[2,3]. In older adults, hearing loss is the third most prevalent chronic condition and the most widespread disability. Its prevalence rises with age – about 46% of people aged 45 to 87 have hearing loss[4].

Cochlear implantation (CI) is a well-established rehabilitation option for patients with severe to profound hearing loss. Language performance after CI is highly variable and depends on many factors, such as age at implantation and intensity of training. However, it has been recognized that even in environments where children are subjected to the same educational programs after cochlear implantation at a similar age, there also remain significant differences in auditory performance that are not attributable to these factors[5]. The underlying etiology and subsequent pathologic changes in the auditory pathway in different groups of children may account for these differences. Cochlear implantation bypasses the affected organ of the corti, stimulates spiral ganglion cells and transmits auditory signals through the central neural pathway to the auditory cortex. Therefore, normal spiral ganglion cells and auditory nerves are critical factors for successful CI. Since the final effect of the underlying etiology in GJB2 mutation-related deafness affects cochlea hair cells, while normal spiral ganglion cell counts are unaffected[6,7], outcomes of CI in these patients are expected to be better than those in non-GJB2-related deafness. However, controversy exists in the literature regarding better auditory and speech performance in cochlear implanted children with GJB2-related deafness, and the overall results have been inconclusive in numerous studies[8,9]. There are no quantitative synthesis based on current evidence regarding the predictive value of a GJB2 mutation on CI outcomes.

As a result of technological modifications in CI devices and due to efforts of legislation and advocacy, indications for cochlear implantation are evolving. In the last decade, there were increasing numbers of studies investigating the efficacy of CI in cases of advanced otosclerosis, which are former candidates of hearing aid and stapedotomy. CI yields a very high success rate in patients with severe to profound sensorineural hearing loss due to advanced otosclerosis[10-14]. Stapedotomy plus hearing aid, a less invasive and much more cost-effective alternative, can also restore acceptable hearing that is comparable to CI in a substantial number of patients[15-20]. It is well known that, although cochlear implant (CI) listeners generally understand speech well in quiet environments, they have particular difficulties understanding speech in the presence of background noise or competing speech[21]. Because of the preservation of acoustic stimulation, if stapedotomy works, patients preserve superior musical perception and sound localization compared to CI recipients. The two treatment policies were compared and debated by many authors, yet, there are no widely accepted guidelines, nor is there any available syntheses of those findings. It is also not very clear whether CI users are capable of perceiving auditory streaming and how they differ from normal hearing listeners in terms of auditory stream segregation.

1.2 Thesis Objectives and Outline

The goal of this thesis is to critically review and synthesize evidence-based findings regarding the prediction of cochlear implantation outcomes. To do so, a targeted systematic review and meta-analysis will be conducted to address the following two specific aims.

Aim 1: To perform a systematic review and meta-analysis that compares stapedotomy versus cochlear implantation for advanced otosclerosis.

Aim 2: To estimate the predictive value of the GJB2 mutation for auditory and speech performance after cochlear implantation in pre-lingual deaf children: systematic review and meta-analysis.

In addition, the thesis will also have the following third aim:

> Aim 3. To clarify whether cochlear implant recipients are capable of perceiving auditory streaming, and to clarify any observed differences from normal subjects.

Following the introduction (Chapter One), the thesis will be divided into six more chapters starting with a background and review of the relevant literature in Chapter Two. The three manuscripts, (i) *Stapedotomy versus Cochlear Implantation for Advanced Otosclerosis; (ii) Predictive Value of GJB2 Mutation Status for Hearing Outcomes in Pediatric Cochlear Implantation;* and (iii) *Auditory Streaming in Cochlear Implant Recipients* will form Chapters Three, Four and Five, respectively. Chapter Six will provide a general discussion and lastly, Chapter Seven will contain the references for this thesis.

CHAPTER TWO: Background and Review of Relevant Literature

2.1 Anatomy and Physiology of Auditory System

Hearing is one of the major senses and, like vision, hearing is important for distant threat detection and communication. It can be used to alert, and to communicate pleasure and fear. It is a conscious appreciation of vibration perceived as sounds. In order to do this, an appropriate signal must reach the higher parts of the brain. The function of the ear is to convert the physical vibration of sound into encoded nervous impulses, which are in turn transmitted to the central auditory pathways. Receiving sound waves, conducting their associated vibrations, and then transducing them into nervous impulses is performed by different parts of the auditory system: the external, middle and inner ear.

2.1.1 External Ear

The parts of the external ear are the pinna and the external auditory canal. The pinna's crinkled shape catches higher frequency sounds and funnels them into the ear canal. The ear canal can be approximated as an acoustic pipe, where the transmission line ends with the acoustic impedance of the tympanic membrane. The interface between the outer and middle ear is the tympanic membrane. It transforms the waves traveling in the air into a mechanical vibration to the auditory ossicles. Shaped like a loudspeaker cone (which is an ideal shape for transmitting sound between solids and air), it is a simple membrane covered by a very thin layer of skin on the outside, a thin lining membrane of the respiratory epithelium tract on the inner surface and a stiffening fibrous middle layer. The whole membrane is less than a 1/10th of a millimeter thick and it covers a round opening into the middle ear cavity.

2.1.2 Middle Ear

The middle ear is an air-filled space connected to the back of the nose by a long, thin tube called the Eustachian tube. The middle ear space houses three small bones, the malleus, incus and

stapes which conduct sound from the tympanic membrane to the inner ear. The purpose of the middle ear is to match the acoustic impedance between the air in the outer ear and the fluid in the inner ear. The characteristic impedance of the fluid is approximately 4,000-fold greater than that of the air. The ossicles act as an impedance transformer that transforms the low pressure and high particle velocity in the air to the high pressure and low particle velocity in the fluid. The function of the middle ear as a transformer is based on the fact that the square area of the stapes (approximately $3mm^2$) is considerably smaller than the square area of the tympanic membrane (approximately 65 mm^2). However, the tympanic membrane does not vibrate like a piston so the equivalent area is much smaller than the physical one. The auditory ossicles also act as a set of levers, whose lever ratio is approximately 1.3. The outer and middle ears amplify sound on its passage from the exterior to the inner ear by about 30 dB. Without the increased pressure at the oval window caused by the middle ear, the oval and the round window would have the same pressure. In this latter case, the resultant sound energy arriving at the inner ear would be very small.

2.1.3 Inner Ear

The function of the inner ear is to transduce vibrations into nervous impulses. While doing so, it also encodes the frequency (or pitch) and intensity (or loudness) analysis of the sound. The cochlea, the essential part of the inner ear for the hearing system, is filled with fluid and is connected to the middle ear through the oval and the round window. The cochlea is a spiral organ that is approximately 2.7 mm in diameter and is about 35 mm long. The basilar and Reisner's membranes run along its length, partitioning the cochlea into three compartments, the scala vestibuli, scala tympani and scala media.

The basilar membrane is a long and narrow membrane whose mass and flexibility change along the membrane. At the window end, it is narrow and light whereas at the apical end it is wider, more flexible and larger. It acts as a mechanical transmission line whose mechanical impedance and the propagation velocity of the wave changes as a function of location. It has several rows of

hair cells that are vibration-sensitive receptors which can convert membraine movement into nerve impulses in the auditory nerves. In total, there are approximately 20,000-30,000 hair cells at an almost regular density along the basilar membrane. Because the properties of the basilar membrane change as a function of location, each part of the membrane reacts differently to sounds with different frequencies. When prolonged high frequencies are contained in the input sound, the traveling wave resonates at the window end of the membrane. At center frequencies, the maximum amplitude of the vibration occurs approximately in the middle of the membrane. When prolonged low-frequency sound is input, then the maximum amplitude of the vibration occurs at the apical end. If the input signal is composed of various frequencies, the traveling wave will create maximum displacements at different points on the basilar membrane. Thus, the cochlea works like a spectrum analyzer, decomposing the input sound signal into its frequency components.

2.2 Cochlear Implantation: Basic principles and History

2.2.1 Basic Principles

A cochlear implantation is an electronic device, which is partially implanted in the cochlea by a surgical procedure to stimulate the auditory nerve. It creates sound sensations in profoundly deaf people for whom a conventional hearing aid can't provide sufficient help. A conventional hearing aid device amplifies the sound, which is then directed to the outer auditory canal, whereas a cochlear implant does not amplify the sound but transforms it to an electrical signal. The external part of the device is worn in the same way as a hearing aid. It produces an electrical stimulus, which bypasses the damaged or missing hair cells in profound sensorineural hearing loss and stimulates the remaining auditory neurons directly.

Although a variety of cochlear implant devices have been developed over the years, they all have the same basic components in common. A microphone picks up the sound and sends it as an electrical signal to a signal processor. The processor modifies the signal according to the

processing scheme in use and sends the processed signal to an external transmitter from where it is transmitted through the skin to an implanted electrode or electrodes. This is usually achieved by using electromagnetic induction or radio-frequency transmission to an internal receiver. One way is also to use a direct connection via a percutaneous plug. Electric current flows between one or more active electrodes and return electrodes, stimulating the auditory nerve thereby creating the sensation of sound. In single-channel implants, only one electrode is used, whereas in multi-channel implants, an electrode array is inserted into the cochlea. Using an electrode array, different groups of auditory nerves can be stimulated at different places in the cochlea - exploiting the place mechanism for frequency coding, so different electrodes are stimulating depending on the signal frequency. In order to make this happen, the input signal has to be decomposed into its frequency components, like in a real cochlea.

2.2.2 The First Bursts of Electric Sound

Although it wasn't until the 1950s that scientists tried, for the first time, to restore hearing by stimulating the auditory nerve directly through surgical electrode implantation, the history of electric stimulation of the hearing organs can be dated back to 1790s to the inventor of the battery, the Italian scientist, Alessandro Volta[22]. By inserting a metal electrode into both his ears, Volta led a direct current with approximately 50 volts through his head in 1800 causing him to have an acoustic experience lasting for seconds[22]. In 1855, Duchenne discovered that auditory stimulation performed with an alternating current provides a longer lasting subjective sound that was more similar to real sounds[23]. During the 1930s, a number of research groups started to investigate the generation of acoustic effects by electrical stimulation of the ear. These studies were based on the above mentioned early reports of electrical stimulation and on reports of electrical phenomena involved in the mechanism of hearing[24]. The first direct evidence of electrical stimulation of the auditory nerve was presented by Andreev et al. (1935): A deaf patient, whose middle and inner ears were damaged, reported hearing sensations during electrical stimulation[25]

2.2.3 First Attempt to Stimulate Auditory Nerve by an Implantable Device

The first attempt to use a surgically implanted device to restore hearing through stimulation of auditory nerve and by bypassing a non-functional cochlea was achieved by Djourno and Eyries on February 25, 1957[26]. They used a handmade receiver made of insulated silver wire wound around an iron core (approx. 2000 turns) covered in Araldite. The electrode contacts were made of stainless steel soldered to the silver coils. The first patient demonstrated improved lip-reading capabilities with the use of this implant. The second patient stopped using the device shortly after surgery[26]. This first success, however, was dampened by the considerable concerns about the safety risk to a patients having an external device inserted into the inner ear.

The American otologist, House, together with a collaborating engineer, Doyle, was inspired by the above mentioned French report. In 1961, House implanted a new electrode array, which was designed to stimulate the cochlea at five different positions along its length into the scala tympani[27]. Unfortunately, it appeared that the silicone that was used contained toxic substances and after about three weeks, the electrode was rejected, resulting in explantation. Although the subject perceived some pleasant and useful hearing sensations, active work on cochlear implantation was temporarily suspended at this point[27,28].

The prospects of developing a safe cochlear implant improved in the late 1960s because of new inventions in various fields, such as cardiac pacemakers (the knowledge of biocompatible materials and the effects of electrical stimulation). With these new technologies, the implants could be used during a prolonged period in patients. The collaboration of technologists in this area also improved, thereby creating a basis for the clinical application of cochlear implants.

In 1971, Simmons and White received a grant from the NIH for the development of cochlear implants. Unlike the House group, Simmons aimed to develop an optimal multichannel implant system[29]. In September 1977, the first patients were implanted with a 4-electrode device which was placed directly into the cochlear nerve. The direct contact with the nerve would yield lower thresholds, less spread of excitation, and less degradation due to neural degeneration[29].

In the late 70s, there was a tendency, based on the early experiments, to employ more-systematic direct electrical stimulation of the auditory nerve in a clinical setting. Then, in the period 1978-1982, a change occurred when industry became involved. In 1982, a group of experts in the United Kingdom recommended the establishment of a limited number of implant centers[30]. In 1984, Clark developed the popular multichannel implant with bipolar stimuli. The experimental status of the cochlear implant changed completely in 1984, when the Food and Drug Administration (FDA) in the United States approved cochlear implants initially for adults, and then for children in 1986[31].

At present, cochlear implantation has become a well-established option to rehabilitate hearing in patients with severe to profound hearing loss. As of December 2012, approximately 324,000 people worldwide had cochlear implants surgically implanted[32].

2.3 Evolution in Candidacy for Cochlear Implantation (CI)

Initially when CI was introduced, the indication for cochlear implantation was limited to adults older than 18 who had profound bilateral sensorineural post-lingual deafness with normal cochlear anatomy. During the last two decades, indications for cochlear implantation have been extended significantly due to (i) technical improvements in engineering and in speech processor design and (ii) accumulated positive experiences in safety and efficacy, which further encouraged the use of cochlear implantation in patients that had not been previously considered as suitable candidates. These changes in candidacy have primarily included: implanting children at younger ages, implanting greater numbers of patients with abnormal cochlea, and implanting patients with increasing amounts of residual hearing.

2.3.1 Cochlear Implantation at Younger Age

The first pediatric cochlear implant program was established at the House Ear Institute in 1980[31], much later than the first adult CI surgery, which had been performed in early 1960s. The primary issue in that era was whether to consider implanting children at all. Universal newborn hearing

screening had led to increased identification of infants with hearing loss worldwide. With the knowlwdge that reproducing the normal auditory experience during infancy, language skills, speech quality and expressive and receptive vocabulary are found to be enhanced by exposure to aural language from as early an age as possible. This increase in early diagnosis led to greater opportunities for early intervention. Numerous studies clearly demonstrated that children implanted at an earlier age outperformed older children[33-36]. This accumulating positive evidence, together with the earlier identification of childhood deafness, has been pushing the age for implantation lower. The FDA approved CI for children in 1986. In June 1990, the Nucleus-22 channel implant received FDA approval for implantation in children aged 2 years and older. The lower limit for age at implantation was kept at 2 years for many years. Then the FDA approved them for 18 months in 1998, and, finally, to 12 months in 2000[34]. Although anatomical and anesthetic concerns, like thin skull bone, intraoperative blood loss and device migration with skull growth present unique risks for implantation at a very young age, no immediate perioperative adverse events or surgical complications have been reported in children implanted under 1 year of age compared with older toddlers[37]. Currently, a growing body of data in auditory perception and linguistic development suggest that children implanted earlier may be more likely to achieve their full potential, and may reduce or eliminate the need for them to "catch up" with their normal hearing counterparts[36]. Therefore, cochlear implantation between ages 6 and 12 months might be become morewidely available soon.

2.3.2 Inner Ear Malformation and Auditory Neuropathy

Although a cochlear malformation was once considered a contraindication, many children with certain types of inner ear malformation currently undergo cochlear implantation. In cases of Mondini dysplasia (IP-II), partial semicircular canal aplasia and large vestibular aqueduct syndrome, CI is usually associated with favorable hearing outcomes. Also, patients with narrow IAC/hypoplasia of bony cochlear nerve canal (BCNC), Michel deformity and common cavity deformity associate with poor CI outcomes may be candidates for an auditory brainstem implant

(ABI)[38].

2.3.3 Preservation of Residual Hearing in the Implanted Ear

In patients with high-frequency hearing loss, preserving residual low-frequency acoustic hearing in the implanted ear has proved to be a practical and effective option in a number of studies[39]. Preservation of low-frequency hearing was attempted by implanting a "newly designed intracochlear electrode, which was smaller both in diameter and length", using a standard-length electrode that was partially inserted into the cochlea combined with "soft surgery" techniques designed to minimize trauma, or inserting a hybrid (short) electrode[40]. Preserved acoustic hearing in the implanted ear can offer certain advantages, including better speech recognition in background noise conditions and better musical appreciation. The improved ability of auditory stream segregation (better speech understanding in background noise) in these patients is primarily a result of improved frequency resolution provided by the combination of acoustic and electric hearing compared to the inherent poor-frequency resolution of electric stimulation.

2.3.4 Bilateral Cochlear Implantation

Although more and more children with a single sided CI are attending mainstream schools, single-sided implantation is not sufficient to facilitate learning at the same rate as students with normal hearing in noisy classrooms. This is because binaural hearing is essential for providing cues that segregate target signals from competing sounds and for sound source localization[41]. The European Bilateral Pediatric Cochlear Implant Forum Consensus Statement, published in 2012, recommended that a deaf infant or child should receive bilateral CIs simultaneously as soon as possible after the definitive diagnosis of deafness to permit optimal auditory development[42]. However, bilateral cochlear implantation may not be recommended in cases of substantial residual hearing in the non-implanted ear, because the use of a hearing aid in the non-implanted ear can represent a potentially beneficial option of bimodal stimulation. Performance in the bimodal condition was significantly better for word recognition and sound localization

compared to the cochlear-implant only and hearing-aid only conditions[43].

2.3.5 Advanced Otosclerosis and Cochlear Implantation

Treatment for advanced otosclerosis has evolved over the past 20 years with the improvement in hearing aid devices and the availability of CI as an alternative option. Stapedotomy is a simple and cost-effective procedure that can achieve satisfactory results in patients with otosclerosis. However, it has been shown that this surgery is not as frequently successful in cases of advanced otosclerosis as in more traditional cases of otosclerosis. CI has a very high success rate and has thus been advocated for patients with advanced otosclerosis in many studies. In the literature, the proposed management policy for patients with advanced otosclerosis is controversial.

2.4 Prognostic of Factors for Uutcomes of Pediatric Cochlear Implantation

During the last decade, an increase in early hearing detection and intervention (EHDI) programs resulting from legislation and advocacy efforts by organizations such as the American Speech-Language-Hearing Association (ASHA) has allowed for the identification of more children who may benefit from cochlear implants. Therefore, the number of pediatric implantees is constantly rising and more children are currently receiving cochlear implantation than adults[44]. Many factors such as age at implantation, duration of implant use, communication mode and family factors are known to impact the hearing and language skills of the implanted child, however, it was noted that many possible prognostic factors have been identified only anecdotally, mostly due to low participant numbers[45]. The literature on prognosis studies is often conflicting with inadequate methodological reporting[46]. In a systematic review on prognostic factors in pediatric CI, Black et al. identified only four factors that influenced pediatric CI outcomes consistently, including age at implantation, presence of inner ear malformations, occurrence of meningitis and GJB2 (Connexin 26) mutation status[47]. In a recent chart-review study by the same authors, the influence of family factors, such as socioeconomic status, parental education and family involvement in the auditory rehabilitation process were also significantly associated with

receptive and expressive language and receptive vocabulary scores[45]. Among these factors, older age at implantation, presence of inner ear malformation, association with meningitis and poor family support adversely influence CI outcomes whereas GJB2-related deafness appearred to predict better speech intelligibility and speech recognition abilities when compared to implanted children with other etiologies of hearing.

2.4.1 Age at Implantation

Language development in children begins at birth and is nearly complete by the age of 6 years. Language skills and expressive and receptive vocabulary is enhanced by exposure to aural language. So, early implantation appears to minimize initial language delays and promotes the development of age-appropriate skills. Considerable evidence has shown that early implantation in children is advantageous and has a positive impact on the development of both receptive and expressive language skills[33-36].

2.4.2 Meningitis

Meningitis is one of the most common causes for postnatal deafness in children; it has been reported that 6-16% of children affected by meningitis will develop profound deafness[48]. In some of these children, as a result of endostial inflammation, new bone may be laid down within the cochlear lumen to cause partial or total obliteration. As a consequence, the complete insertion of cochlear electrode becomes difficult. A number of studies demonstrated that post-meningitic deaf children showed significant improvement in their auditory receptive abilities if implanted early[49-50]. However, audiologic outcomes are difficult to predict, especially in the presence of cochlear ossification[48].

2.4.3 Inner Ear Malformation

Although inner ear malformation was once considered as a contraindication for cochlear implantation, it has been reported that most children with less severe malformations, including partial semicircular canal aplasia, incomplete partition and large vestibular aqueduct syndrome

were usually associated with excellent CI outcomes, whereas patients with narrow IAC/hypoplasia of bony cochlear nerve canal (BCNC), Michel deformity and common cavity deformity associate were usually associated with poorer CI outcomes[38].

2.4.4 Family Environment

Many studies have reported that family factors and maternal education can impact the vocabulary and language ability of an implanted child[51-57]. Similarly, evidence shows that children with less parental involvement in the auditory rehabilitation process had significantly poorer speech and language acquisition[58,59]. Some other family factors, including families' urban location, socioeconomic status and parental stress, can influence the outcomes of pediatric cochlear implantation[60-62]. Given the results of these studies, it is clear that family environment was a predictor of receptive and expressive language outcomes following pediatric CI.

2.4.5 GJB2 Gene Mutation

Gap Junction Beta-2 or the GJB2 gene, which resides at chromosomal location 13q11 and encodes for the protein connexin 26, is a major contributor in a large percentage of non-syndromic deafness[63,64]. Previously, it has been considered that GJB2 mutations disrupt intercellular potassium recycling, which results in hair cell dysfunction and deafness.[65] However, more recent evidence showed that hair cell degeneration may not be the primary cause for deafness in GJB2-related hearing loss. The alteration of micromechanical properties of supporting cells which in turn reduce the electromotility of outer hair cells and active cochlear amplification are more related to the pathophysiology of GJB2 mutation-related hearing loss[66]. Because normal spiral ganglion cells and auditory nerves are preserved in a GJB2 mutation[67], which is a critical factor for successful CI, outcomes of CI in these patients are expected to be better than those in non-GJB2-related deafness[46].

2.4.6 Linking Statement for the Next Part

Management of advanced otosclerosis has evolved over the past 20 years with the improvements

in hearing aid devices and the availability of CI as an alternative option to stapedotomy. Stapedotomy is not as frequently successful in cases of advanced otosclerosis as in more traditional cases of otosclerosis. CI has a very high success rate and has thus been advocated for advanced otosclerosis in many studies. In the literature, the proposed management policy for patients with advanced otosclerosis is controversial. A systematic review of stapedotomy versus CI for patients with advanced otosclerosis appears to be warranted, and will be presented in the next chapter.

CHAPTER THREE: Stapedotomy versus Cochlear Implantation for Advanced Otosclerosis (Manuscript 1)

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3.1 Abstract

Objectives To compare the hearing outcomes of stapedotomy versus cochlear implantation in patients with advanced otosclerosis.

Data Source PubMed, EMBASE, and The Cochrane Library were searched for the terms "otosclerosis", "stapedotomy" and "cochlear implantation" and their synonyms with no language restrictions up to March 10, 2015.

Methods Studies comparing the hearing outcomes of stapedotomy with cochlear implantation and studies comparing the hearing outcomes of primary cochlear implantation with salvage cochlear implantation after an unsuccessful stapedotomy in patients with advanced otosclerosis were included. Postoperative speech recognition scores were compared using the weighted mean difference and a 95% confidence interval.

Results Only four studies met our inclusion criteria. Cochlear implantation leads to significantly better speech recognition scores than stapedotomy ($p < 0.0001$). However, this appears to be due to the variability in outcomes after stapedotomy. Cochlear implantation does not lead to superior speech recognition scores when compared with the subgroup of successful cases of stapedotomy plus hearing aid ($p = 0.47$). There is also no significant difference with respect to speech recognition between primary cochlear implantation and those secondary to a failed stapedotomy ($p = 0.22$).

Conclusions: Cochlear implantation leads to a statistically greater and consistent improvement in speech recognition scores. Stapedotomy is not universally effective; however, it yields good results comparable to cochlear implantations in at least half of patients. For cases of unsuccessful stapedotomy, the option of cochlear implantation is still open and the results obtained through salvage cochlear implantation are as good as those of primary cochlear implantation.

Keywords: Otosclerosis; Stapedotomy; Cochlear implantation; Speech recognition.

3.2 Introduction

Otosclerosis is an aberrant process of bone resorption of the labyrinthine capsule followed by reparative deposition of new, immature sclerotic bone. The most commonly affected location is around the oval window (fenestral otosclerosis), which results in conductive hearing loss due to stapes footplate fixation. As it undergoes a maturation process, the sclerotic bone increases in size and depth[68]. In approximately 10% of patients, otosclerotic foci invade deeper into the labyrinth, resulting in retrofenestral otosclerosis; this process gradually leads to severe mixed hearing loss and then to profound sensorineural hearing loss (SNHL)[69]. Several studies have indicated that retrofenestral sclerotic foci may lead to hearing loss through disturbance of the ionic homeostasis of the cochlea by hindering ion recycling and reducing the endocochlear potential. This leads to dysfunction or loss of cochlear hair cells[70,71]. SNHL may also be caused by lytic enzymes that are released from otosclerotic foci into the perilymph, altering its normal composition, or by narrowing of the cochlear lumen with resultant distortion of the basilar membrane[72,73].

Far advanced otosclerosis (FAO) was first defined by House and Sheehy[74] in the 1960s as an air conduction threshold of more than 85 dB and an immeasurable bone conduction threshold (due to the limitations of the audiometer at that time). In the current era of cochlear implantation (CI), speech discrimination scores are more likely to be used than pure-tone thresholds. Therefore, the definition of FAO is no longer applicable and the term “advanced otosclerosis” is often used to describe otosclerotic patients with profound SNHL and decreased speech recognition abilities[75].

In the literature, the proposed management policy for patients with profound SNHL and severely decreased speech recognition abilities due to otosclerosis is controversial. Stapedotomy is a simple and cost effective procedure that can achieve satisfactory results in patients with otosclerosis. Numerous authors have shown that stapedotomy followed by use of a hearing aid can restore acceptable hearing, even in advanced otosclerosis with profound SNHL[15-20]. However, there is also evidence that this surgery is not as frequently successful in cases of advanced otosclerosis as in more traditional cases of otosclerosis. CI has a very high success rate

and has thus been advocated for patients with advanced otosclerosis in many studies[10-14.] To our knowledge, there is no systematic review that summarizes the existing comparative studies.

3.3 Materials and Methods

3.3.1 Inclusion Criteria

Types of Studies. Only comparative studies between stapedotomy and CI with respect to post-operative hearing outcomes were included. The exception was the inclusion of studies that compared the outcomes of primary CI with salvage CI after an unsuccessful stapedotomy. Conference abstracts, animal studies, comments, case reports, and review articles were excluded.

Types of Participants. Patients with profound SNHL and decreased speech recognition abilities due to otosclerosis.

Types of Interventions. Stapedotomy with postoperative hearing aids and CI.

Types of Outcome Measures. Speech recognition tests including word recognition scores (WRS) and sentence recognition scores.

3.3.2 Search Methods for Identification of Studies

Systematic searches for eligible studies were conducted in PubMed, EMBASE and The Cochrane Library. There were no language or publication year restrictions. The following search strategy was used to identify eligible studies:

1. The search terms otosclerosis OR otoscleroses OR otospongiosis OR otospongioses were used in all three databases, and all papers with these terms were retrieved.

2. The same process was conducted using the terms stapedotomy OR stapedectomy OR stapedotomies OR stapedectomies OR "stapes surgery".

3. The final set of search terms were "cochlear implant" OR "cochlear implantation" OR "cochlear implants" OR "cochlear implantations" OR "cochlear prosthesis" OR "cochlear prostheses".

4. Any studies that contained at least one of the search terms from each of the three previous steps (1 AND 2 AND 3) were retained for screening.

Eligible publications were identified by two researchers independently. Titles and then abstracts were screened, and if they appeared to meet the inclusion criteria, full texts were retrieved and evaluated in detail. Screening and evaluation of studies were performed using EndNote X7.

3.3.3 Data Extraction

Data were collected from each included study using a data extraction form that included the following fields: inclusion criteria, study design, study population, interventions, outcome measures, criteria for success, tool(s) for assessing audiological performance, and time of assessment.

3.3.4 Quality Assessment and Data Synthesis

The quality of included studies was assessed based on whether: ethical approval was obtained, the design was prospective, eligibility criteria were specified, a power calculation was applied, appropriate controls were used, appropriate outcome measures were used, confounding factors were reported and controlled, appropriate analyses were made, and any missing data was accounted for. The level of evidence of each study was rated based on its design and quality according to the criteria of the Oxford Centre for Evidence-based Medicine's Levels of Evidence (2009)[76]. Data synthesis was performed by Review Manager 5.3. Continuous outcome variables were compared using weighted mean differences and 95% confidence intervals (CIs). Because of the heterogeneity between outcome measures, a random effect model was used for data pooling.

3.4 Results

Our search strategy identified 92 articles in total, of which only four studies met our predefined inclusion criteria[19,77-79]. The flow chart of the study selection process is shown in Figure 3-1.

3.4.1 Study Characteristics and Methodological Quality

The design of all included studies was retrospective case control or case series. The characteristics and level of evidence of the included studies are shown in Table 3-1, and the methodological quality of the studies is displayed in a 100% stacked bar chart (Figure 3-2).

Criteria for patient selection. Patient selection criteria varied across the included studies. In Berettini et al[79], the inclusion criteria were air conduction (AC) thresholds below 110dB and 118dB for stapedotomy and CI, respectively, and aided word recognition scores (WRS) less than 15% for stapedotomy and 4% for CI. In the study by Calmels et al[19], the inclusion criteria were aided WRS below 30% at 65dB and blank diagram (immeasurable air and bone conduction) for both treatment groups. Kabbara et al[77] used the criteria of AC below 85dB and aided WRS below 50% at 60dB for both treatment groups. In one study, audiometric criteria for patient selection was not clearly specified, but it is obvious from the paper that all patients had advanced otosclerosis based on positive findings on CT scanning (n = 27) and/or previous surgery for otosclerosis (stapedotomy in 18 and fenestration in 2 patients)[78]. In all studies, radiologic criteria were also specified, with positive findings of otosclerotic foci on high resolution temporal bone CT.

Table 3-1. Study characteristics and level of evidence

Study	Stapedotomy		Cochlear Implantation		Success criteria	Outcome measures	Time of assessment (months)	Design	Level of evidence
	n	SR (%)	n	SR (%)					
Berrettini 2004[79]	6	61±28	5	98 ±2.45	aided telephone conversation	WRS, PTA	12	retro	4
Marshall 2005[78]	-	-	30	75	Not clear	CID, HINT	12	retro	4
Calmels 2007[19]	11	35±36.3	7	80 ±14	Aided telephone use & self satisfaction	WRS	12	retro	4
Kabbara 2015[77]	32	51±34	34	73±19	aided WRS>50% (no longer be candidate for CI)	WRS, PTA	12	retro	3b

n: number of patients; SR: speech recognition; WRS: Word Recognition Score; PTA: Pure Tone Audiometry; CID: Central Institute for the Deaf sentence test; HINT: Hearing in Noise Test; retro: retrospective study

Criteria for success. Surgical success criteria also varied across studies. Two studies defined success as the ability to aided telephone conversation[19,79], one defined success as aided WRS > 50% plus subsequent ineligibility for CI[77], and another study did not clearly specify any criteria[78].

Table 3-2. Subgroup analysis: stapedotomy (success & failure), CI (with vs without stapes prosthesis)

Study	Stapedotomy				Cochlear implantation			
	Success		Failure		Salvage (with previous stapes prosthesis)		Primary (without previous stapes prosthesis)	
	n	SR (%)	n	SR (%)	n	SR (%)	n	SR (%)
Berrettini 2004[79]	4	80 ±10.6	2	22.5±2.5	-	-	-	-
Marshall 2005[78]	-	-	-	-	18	82 ±16	12	72± 15
Calmels 2007[19]	4	80 ±10	7	8 ±10	4	85± 11	3	74 ±15.5
Kabbara 2015[77]	19	76 ±16	13	14 ±12	25	72± 20	9	75±17

n: number of patients; SR: speech recognition

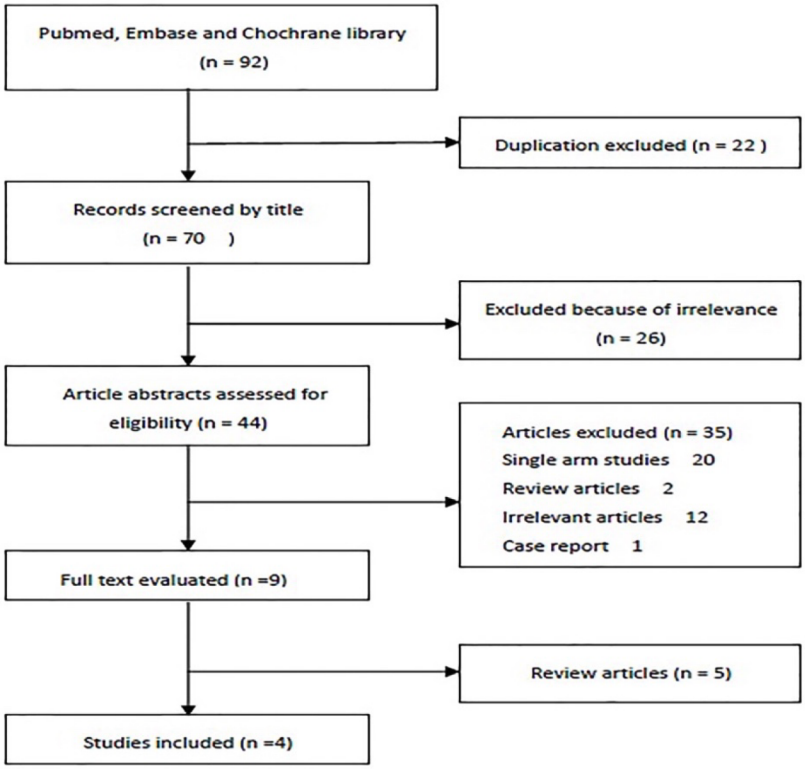

Figure 3-1. Flow diagram of search and study selection process.

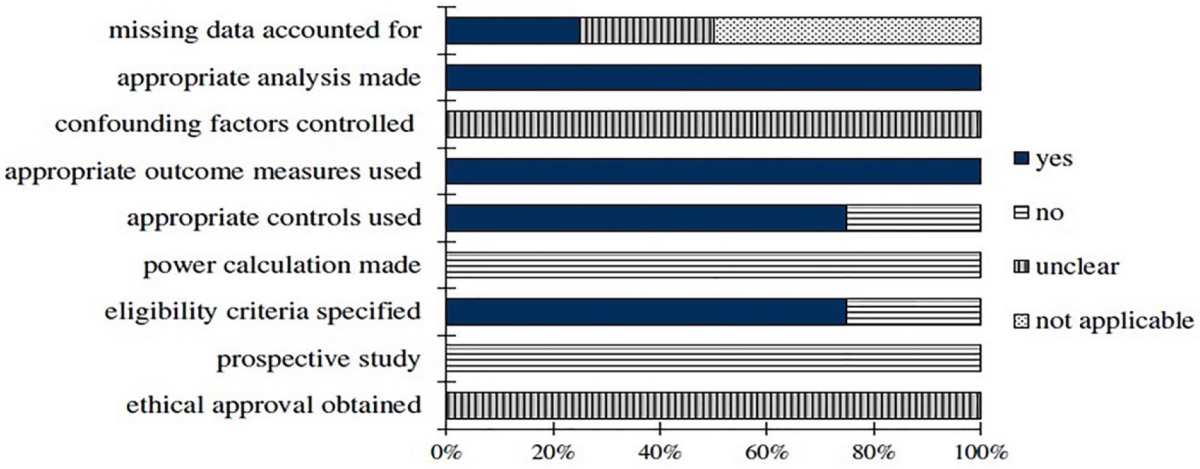

Figure 3-2. Methodological quality of the included studies.

3.4.2 Outcome Measures

The outcome measure was WRS in three studies[19,77,79] and sentence recognition scores (Central Institute for the Deaf sentence test and the Hearing in Noise Test) in one study[78]. Pure tone audiometry (PTA) results were reported for only two studies[77,79].

Stapedotomy vs. Cochlear Implantation. The meta-analysis showed that the difference between stapedotomy and CI with respect to WRS was statistically significant and favoring CI (total mean difference: -31.79, 95% CI: -46 to -17.59, $p < 0.0001$; Figure 3-3A).

Successful Stapedotomy plus Hearing Aid vs. Cochlear Implantation. In one study[77], successful and unsuccessful cases of stapedotomy were analyzed separately to find possible predictors of good outcomes. In two other studies[19,79], it was possible to analyze the favorable and unfavorable outcomes of stapedotomy separately since original data was available. Therefore, we compared the outcome of successful cases of stapedotomy with CI (Table 3-2). The meta-analysis showed that the difference between successful stapedotomy plus hearing aid and CI with regard to post-operative speech recognition was not statistically significant (total mean difference: -5.14, 95% CI: -18.95 to 8.67, $p = 0.47$; Figure 3-3B).

Primary Cochlear Implantation vs. Salvage Cochlear Implantation. Post-operative speech recognition scores for primary CI and salvage CI secondary to an unsuccessful stapedotomy (stapes prosthesis present at the time of surgery) were also compared in three studies (Table 2)[19,77,78]. The meta-analysis comparing those two subgroups showed that the difference between primary and salvage CI was not statistically significant (total mean difference: 5.58, 95% CI: -3.35 to 14.51, $p = 0.22$; Figure 3-3C).

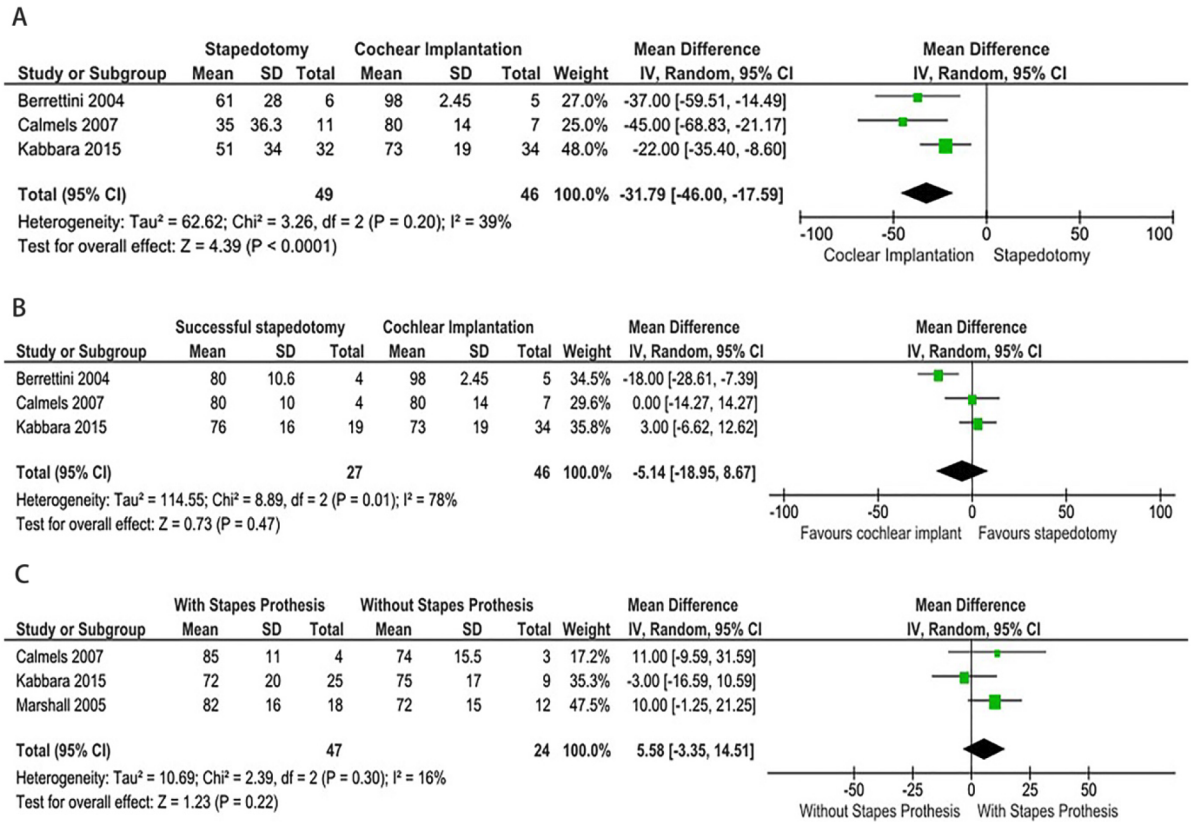

Figure 3-3. Postoperative speech recognition score: (A) Stapedotomy vs. Cochlear Implantation, (B) Successful Stapedotomy vs. Cochlear Implantation, (C) Cochlear Implantation with Stapes Prosthesis vs. Cochlear Implantation without Stapes Prosthesis.

3.5 Discussion

The results of our meta-analyses showed that CI definitely leads to significantly better speech recognition scores than stapedotomy. The outcomes of CI were consistently good in all reported patients. This supports the opinion that the outcomes of CI are more predictable and consistent. Favorable outcomes for CI in the majority of patients with advanced otosclerosis are not unexpected, since adults who have severe to profound hearing loss and who lost their hearing after speech and language development are the ideal candidates for CI.

When we compared the results of CI with the subgroup of successful cases of stapedotomy plus a well-fitted hearing aid, meta-analysis revealed that there was no significant difference with respect to post-operative speech recognition between CI and stapedotomy. This indicates that treatment with stapedotomy followed by a well-fitted hearing aid allows a considerable number of patients with advanced otosclerosis (4 out of 6, 4 out of 11 and 19 out of 32 patients, respectively, in the three included studies) to achieve good speech recognition, comparable to those treated with CI.

To ascertain whether or not the presence of a previous stapedotomy has a negative impact on the outcome of subsequent CI, we compared post-operative speech recognition between primary CI and salvage CI secondary to an unsuccessful stapedotomy. Meta-analysis showed that the difference was not statistically significant, suggesting that the presence of a previous stapes prosthesis does not have any negative impact on salvage CI. In Figure 3-3C, it is evident that, although not significant, there is a clear trend favoring CI with a previous prosthesis. This is not because the previous prosthesis has a favorable effect on subsequent CI, but because most patients who were previously treated with stapedotomy tend to have less severe hearing loss.

3.5.1 Intervention for Advanced Otosclerosis

Treatment for advanced otosclerosis has evolved over the past 20 years with the improvement in hearing aid devices and the availability of CI as an alternative surgical option[77]. Our systematic review indicates that correction of the conductive component of mixed hearing loss by stapedotomy followed by a hearing aid can be effective enough to achieve acceptable hearing for some patients. However, the results of stapedotomy for advanced otosclerosis in the included studies were quite variable — "very good in some cases but unsatisfactory in others"[79]. The overall success rate of stapedotomy in this systematic review is 55%, and in the general literature, the reported success rates range between 36% and 89%[19,80]. Unlike the variable outcomes of stapedotomy, CI in patients with advanced otosclerosis consistently yields excellent results with regard to speech recognition[75,79]. However, it is a much more expensive and complex procedure that involves surgical and postoperative programming challenges[79,81], and because of

ossification and cochlear hyper density, problems such as extra drilling, incomplete insertion or misplacement of electrode array also have to be taken into account[77,82].

In weighing the options between CI and stapedotomy, one also has to consider that stapedotomy has some advantages over CI. First, it is a less invasive procedure that can be performed endoscopically through a transcanal approach. The procedure can be performed under local anesthesia, which is an especially relevant benefit for the elderly and patients with comorbidities[19,83,84]. Second, it is a less costly operation with minimal post-operative requirements (fitting of a hearing aid). As mentioned above, CI is much more expensive and much more demanding post-operatively, requiring intensive rehabilitation and programming. Third, because of acoustic stimulation, the quality of sound is more natural and music perception can be better preserved after stapedotomy[83]. Lastly, in case of failure, the presence of a previous stapes prosthesis does not have any negative impact on subsequent salvage cochlear implantation.

Given the uncertainty regarding the best surgical approach, Merkus et al introduced an algorithm based on speech recognition, CT classification, and the extent of the air-bone gap (ABG) to guide surgeons to either CI or stapedotomy for patients with advanced otosclerosis[75]. In this algorithm, CI is proposed for patients with speech recognition scores < 30%. If scores are between 30% and 50%, treatment may be CI or stapedotomy. In cases of severe retrofenestral otosclerosis on CT, CI is proposed, whereas if the CT scan shows less retrofenestral involvement, the ABG would guide the surgeon to either stapedotomy or CI. If the ABG is 30 dB or more, stapedotomy is recommended as a cost-effective option with good chances for improvement of hearing. If the ABG is less than 30 dB, patients should be treated with CI rather than stapedotomy. On the surface, this algorithm appears to be a reasonable way to determine which surgical treatment should be performed. However, retrospective evidence suggests that CT findings (extent of retrofenestral sclerosis) and pre-operative residual hearing (as measured by both pure tone audiometry and speech recognition) are not sensitive or specific enough to predict

the outcomes of stapedotomy[77,83]. Moreover, there is evidence that, even in patients with unmeasurable air and bone conduction thresholds (a "blank" audiogram) and 0% speech recognition, stapedotomy followed by a hearing aid can still lead to a good result in up to 30% of patients[19,77].

Because of the advantages listed above, stapedotomy seems to be worth trying before considering CI in patients with advanced otosclerosis. However, the outcomes of stapedotomy are quite variable compared to CI and are difficult to anticipate because of the paucity of reliable predictive factors[75,83]. Patients with less retrofenestral sclerosis, previous benefit from hearing aid use, and speech recognition scores above 50% have a higher success rate, whereas severe retrofenestral sclerosis with basal turn ossification and speech recognition scores less than 30% have been associated with a lower success rate[77]. The variability in outcomes and the limitations of our study restrain us from making a solid recommendation. Treatment decisions rest on surgeons and informed patients, who should receive adequate counseling regarding the factors covered here.

3.5.2 Limitations of This Systematic Review

As secondary research and as in any other systematic review, our review was limited by the quantity and quality of available literature. Although patient inclusion criteria in all studies met the criteria of advanced otosclerosis, there were some differences. One limitation of this systematic review is that because there were only 3 studies available in each compared domain (stapedotomy vs CI, successful stapedotomy 1 hearing aid vs CI and primary vs salvage CI), it was not possible to perform a subgroup analysis according to speech recognition score in the inclusion criteria among these studies. In the studies included in the meta-analysis of primary vs salvage CI, the outcome measures were WRS in 2 studies and sentence score in 1 study. Although both WRS and sentence recognition score are both indicative of speech recognition, individual words are not equivalent to words presented in sentences, the former being more challenging than the latter due to the redundancy of information in sentences. All these

heterogeneities may have produced biases. In addition, the retrospective nature of the included studies and their small sample sizes limit the level of evidence that can be provided by our systematic review.

3.6 Conclusion

CI leads to a statistically greater and consistent improvement in speech discrimination scores when compared to stapedotomy. Stapedotomy is not universally effective; however, it yields results comparable to CI in at least half of patients. For cases of unsuccessful stapedotomy, the option of CI is still open and the results obtained by a salvage CI are as good as those of CI when no prior stapedotomy was performed. Surgeons and their patients need to be aware of the results of our study and of its limitations when making an informed decision regarding treatment.

3.7 Linking Statement to The Next Chapter

It has been well recognized that even in environments where children are subjected to the same educational programs after cochlear implantation at a similar age, there still remain significant differences in language performance. The underlying etiologies and subsequent pathological changes in the auditory pathways of different patient population may account for the variable CI outcomes. The next chapter will continue to critically review and synthesize evidence-based findings regarding the prediction of CI outcomes, this time by examining the association of GJB2 mutation status in the implanted child.

CHAPER FOUR: Predictive Value of GJB2 Mutation Status for Hearing Outcomes of Pediatric Cochlear Implantation (Manuscript 2)

Otolaryngology – Head and Neck Surgery (current status: first round of minor revisions)

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4.1 Abstract

Objective To systematically review and quantify current evidence regarding the association of the GJB2 mutation status with outcomes of pediatric cochlear implantation.

Data Sources PubMed, EMBASE, and The Cochrane Library were searched for "GJB2", "pediatric hearing loss" and "cochlear implantation" and their synonyms, with no language restrictions until December 2, 2015.

Methods Studies investigating the predictive value of the status of GJB2 mutation for outcomes of pediatric cochlear implantation were included. Speech recognition scores and other outcome measures assessing the impact of the GJB2 mutation status were pooled using weighted mean differences, and a 95% confidence interval.

Results Eighteen studies met the inclusion criteria. The difference between GJB2-related deafness and non-GJB2-related deafness due to unidentified causes and other types of genetic deafness without additional disabilities was not statistically significant; however, the difference between GJB2-related deafness and acquired hearing loss due to environmental etiologies was statistically significant and favours GJB2-related deafness.

Conclusions GJB2-related deafness leads to significantly better CI outcomes when compared to acquired deafness caused by environmental etiologies. However, if patients are matched carefully with respect to factors known to affect language development and speech perception, carrying the GJB2 mutation does not suggest a better prognosis than those whose deafness results either from non-syndromic hearing loss of unknown origin, or other types of genetic mutations in the absence of additional neurological deficits.

Keywords GJB2, Connexin 26, Pediatric hearing loss, Cochlear implantation.

4.2 Introduction

Approximately 1 to 6 out of every 1,000 children globally are born with severe-to-profound sensorineural hearing loss[2,3]. About 50-60% of all these cases are considered to be of genetic origin, but the actual percentage is probably higher because a significant amount of hearing loss is attributed to unknown or sporadic causes[85,86]. Among hereditary deafness, autosomal non-

syndromic recessive hearing loss accounts for up to 80% of all cases[63,64]. To date, 125 genes have been reported to be involved in non-syndromic hearing loss[87]. Among them, the Gap Junction Beta 2 or GJB2 gene, which resides at chromosomal location 13q11 and encodes for the protein connexin 26, has turned out to be a major contributor in a large percentage of non-syndromic deafness[63,64]. Connexin 26 is a member of the family of related gap-junction channel forming proteins expressed in the cochlea and in the epidermis. The exact underlying mechanism of GJB2 mutation-related hearing loss is not very clear. Previously, it has been considered that GJB2 mutations disrupt intercellular potassium recycling which results in hair cell dysfunction and deafness[65]. However, more recent evidence showed that hair cell degeneration may not be the primary cause for deafness in GJB2-related hearing loss; rather, the alteration of micromechanical properties of supporting cells which in turn reduce the electromotility of outer hair cells and active cochlear amplification are more related to the pathophysiology of GJB2 mutation-related hearing loss[66].

Cochlear implantation (CI) is a well-established option to rehabilitate hearing in children with severe to profound deafness. Language performance after cochlear implants is highly variable and depends on many factors, such as age at implantation, amount of residual hearing, and intensity of training[10,11,88,89]. However, even in environments where children are subjected to the same educational programs after cochlear implantation at a similar age, significant differences remain in auditory performances that are not attributable to age of implantation or amount of training[12]. The underlying etiology and subsequent pathologic changes in the auditory pathway in different groups of children may account for these differences. Cochlear implantation bypasses the affected organ of Corti, stimulates spiral ganglion cells and transmits auditory signals through the central neural pathway to the auditory cortex; therefore, normal spiral ganglion cells and auditory nerves are critical factors for successful CI. Since the final effect of underlying etiology in GJB2 mutation-related deafness is affecting cochlea hair cells while normal spiral ganglion cell counts are preserved[13,14], outcomes of CI in these patients are expected to be better than those in non-GJB2-related deafness. In numerous publications, CI

outcomes in children with GJB2-related deafness have been compared with a control group of non-GJB2-related deafness, however, the overall results have been inconclusive and controversial. Carrying GJB2 mutation was even reported to be associated with poorer CI outcomes in some studies[8,9]. In this systematic review, we assessed and quantified current evidence regarding the predictive value of GJB2-mutation status on the outcomes of pediatric CI.

4.3 Materials and Methods

4.3.1 Inclusion Criteria

Types of studies: Studies comparing the hearing and speech performances after cochlear implantation between groups of GJB2-related deafness and non-GJB2-related deafness were included. Single arm studies, animal studies, comments, case reports, letters, and review articles were not included. Studies with incomplete or non-extractable data were also excluded.

Types of participants: The study population was limited to pediatric patients with pre-lingual hearing loss.

Types of interventions: Cochlear implantation.

Types of outcome measures: Speech recognition score (word and sentence), Infant Toddler Meaningful Auditory Integration Scale (IT -MAIS), Speech Intelligibility Rating (SIR), and Categorized Auditory Performance (CAP).

4.3.2 Search Methods for Identification of Studies

PubMed, EMBASE and The Cochrane Library were searched systematically with no restrictions of language or publication year, until December 2015. Potentially eligible publications were identified via an electronic search according to a specific search strategy, then article abstracts were screened manually when established to satisfy the inclusion criteria; full text articles were retrieved and a detailed assessment was performed for eligibility. The screening and evaluation process was performed with EndNote X7.

The following search strategy was used to identify eligible studies:

1. The search terms GJB2 OR "GJB 2" OR connexin26 OR "connexin 26" OR DFNB1 were used in all three databases, and all papers with any of these terms were retrieved.
2. The same process was conducted using the terms "pediatric population" OR pediatrics OR children OR child OR kid OR kids.
3. The final set of search terms were "cochlear implant" OR "cochlear implantation" OR "cochlear implants" OR "cochlear implantations".
4. Any studies that contained at least one of the search terms from each of the three previous steps (1 AND 2 AND 3) were retained for screening.

4.3.3 Data Extraction and Synthesis

Data was collected from each included study using a data extraction form. The following information was collected: study design, inclusion criteria, GJB2 mutation status, etiology of deafness, size of study population, interventions, outcome measures for auditory and speech performance, and time of assessment after implantation. Attempts were made to contact authors of the studies with incomplete data; only one reply with relevant data was received.[19] Data synthesis was performed with Review Manager 5.3. Continuous outcome variables were compared using weighted mean differences and 95% confidence intervals; a random effect model was used for data pooling.

4.3.4 Quality Assessment and Level of Evidence

The quality of included studies was assessed based on whether it was a prospective study, with an ethical approval was obtained, when its eligibility criteria was clearly specified, whereby appropriate controls were used, with appropriate outcome measures were used, the confounding factors were reported and controlled, any missing data was accounted for, and any limitations were discussed. The level of evidence of each study was rated by its design and quality according to the criteria of the Oxford Centre for Evidence-based Medicine – Levels of Evidence (2009)[7]

4.4 Results

Our search strategy identified 164 articles in total. After removing duplication, 97 of them were screened for eligibility. Following screening and detailed assessment, 18 articles were identified as meeting the inclusion criteria and included in this systematic review. The flow chart of the study selection process is shown in Figure 4-1.

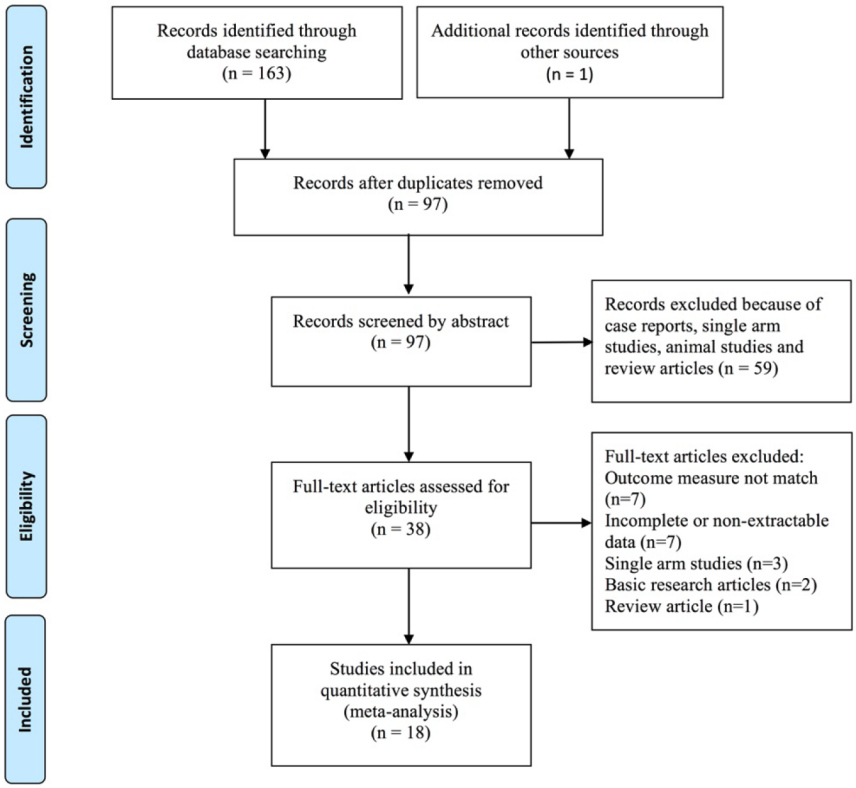

Figure 4-1. Flow diagram of the study selection process

4.4.1 Study Characteristics and Methodological Quality

All the 18 included studies were observational cohorts or case control studies, and only 3 of them were prospective in a study design. Characteristics and level of evidence of the included studies

were shown in Table 4-1. Methodological quality of the studies was displayed in a 100% stacked bar chart, as shown in Figure 4-2.

4.4.2 Genetic Analysis

Methods for genetic analysis were reported in 13 studies. Various methods including DNA sequencing[86,90,92,93,95,96,101], denaturing gel electrophoresis[63,94,97] and denaturing high-performance liquid chromatography[91,98] were applied for mutation analysis for GJB2. In some studies, the 35delG mutation was detected by an allele-specific PCR[86,100] or by restriction-enzyme digestion of the PCR product[91]. DNA was isolated from venous blood in most studies while buccal smear/mouth wash samples were used in some studies[91-94]. GJB2 mutation positivity was defined as a biallelic mutation in 11 studies[63,89-93,95,97-99,101], both single or multiple alle mutation in 3 studies[10,86,96] and no detailed information were provided in the remaining 4 studies[9,94,100,102].

Table 4-1. Characteristics and level of evidence of the included studies

Author /Year	GJB2		Non-GJB2			Outcome Measures: GJB2 vs. Non-GJB2 (Mean ± Standard Deviation)	Age at Evaluation (m)	Study Design	LE
	n	Age at Implant (m)	n	Age at Implant (m)	Etiology				
Fukushima 2002[90]	3	47	4	46	Low birth weight (2), unknown (2)	Word score: 67±1.5 vs. 47±32	58	retro	3b
Matsushiro 2002[63]	4	39	11	48	Unknown	IT-MAIS: 27.5±1.3 vs. 17.6±3.9	54	retro	3b
Dahl 2003[91]	11	54	11	54	Unknown	Sentence score:82.6±16.3vs.84.5±14 Word score: 66.1±19.5 vs. 68.0±16.6	90	retro	3b
Cullen 2004[86]	20	39	27	38	Not specified	Word score:91±12 vs.47±44	63	retro	3b
Sinnathuray 2004[92]	12	46	20	69	Unknown	SIR: 2.83±0.83 vs. 2.05±0.88	82	retro	3b
Sinnathuray 2004[93]	9	46	19	69	Unknown	Word score: 82±32 vs. 54±38 Sentence score: 70±30 vs. 42±36	82	pros	3b
Kawasaki 2006[94]	3	54	5	54	Unknown (3), CMV(1), ADHD(1)	Sentence score:96.6±1.15 vs. 93.6±3	108	retro	3b
Taitelbaum 2006[95]	5	46	5	44	Not specified	Word score: 73±22 vs. 78±6 Sentence score: 85±12 vs. 95±4 IT-MAIS: 32±9 vs. 31.5±11	81	retro	3b
Wu 2008[96]	4	38	45	45, 18	Unknown (45) SLC26A4 (18)	GJB2 vs. Unknown: Word score:73.5 ±6.8 vs. 56.3±34.4 Sentence score: 93.3±5 vs. 58.3±37 GJB2 vs. SLC26A4: Word score: 73.5 ±6 vs. 79.2±10 Sentence score: 93.3±5 vs. 89.9±10	106	pros	3b
Lalwani 2009[9]	3	112	30, 6	112	Unknown (30), Other genetic(6)	GJB2 vs. Unknown (word score): 74±7.55 vs. 85.77±22.66 GJB2 vs. Other genetic (word score): 74±7.55 vs. 93±9.76	141	retro	3b
Liu 2009[97]	10	84	10	84	Unknown	Sentence score: 89 ±10 vs. 90 ±7 IT-MAIS: 37.1 ±2.9 vs. 35.3 ±6. 9 CAP: 7.0 ±0.9 vs. 6.9 ±1.2 SIR: 4.3 ±1.2 vs. 3.6 ±1.3	108	retro	3b
Reinert 2010[89]	13	Not given	15, 16	Not given	Other genetic mutations (15) Non genetic (meningitis, CMV, rubella, etc.) (16)	GJB2 vs. Other mutation (word): 99 ±2.70 vs. 96±8.77 GJB2 vs. Non genetic (word score): 99 ±2.70 vs. 87 ±21.6	42m (post op)	retro	3b
Daneshi 2011[98]	33	66	36	66	Unknown	CAP: 7.30 ±0.68 vs. 7.54 ±0.56 SIR: 3.27 ±0.67 vs. 3.64 ±0.08	84	retro	3b
Wu 2011[10]	12	38	22, 75	48	SLC26A4 (22), Non genetic unknown (75)	GJB2 vs. SLC26A4 (CAP): 6.1±1.2 vs. 6.7±0.5 GJB2 vs. Non genetic (CAP): 6.1±1.2 vs. 5.6±1.3	79	pros	2b
Yoshida 2013[99]	9	37	10	36	Unknown	IT-MAIS: 33.6 ± 7.8 vs. 30.4 ± 7.6	60	retro	3b
Cai 2014[100]	40	34	80	26	Unknown	CAP: 7.2 ±0.6 vs. 7.2±0.7 SIR: 4.2 ±0.6 vs. 4.1±0.1 IT-MAIS: 35.7±3.5 vs. 35.4±4	42	retro	3b
Varga 2014[101]	40	42	17, 24	46	Known etiology (intrauterine infection &meningitis etc.) (17) Unknown (24)	GJB2 vs. Known: Word score: 64.3±31.6 vs. 26±31 CAP: 5.8±1.4 vs. 4.6± 2.2 GJB2 vs. Unknown: Word score: 64.3±31.6 vs. 44.4±32.8 CAP: 5.7±1.3 vs. 5.1±1.2	80	retro	3b
Hani 2015[102]	21	28	17	38	Prematurity (6), CMV(3), meningitis (2) and others	Word score: 92.67±14.17vs.90±13.0 Sentence score: 85.2±4.3vs.68±19.2	57	retro	3b

n, number; m, month; IT–MAIS, infant toddler meaningful auditory integration scale; CAP, categorized auditory performance; SIR, speech intelligibility rating; CMV, cytomegalovirus infection; ADHD, attention deficit hyperactivity disorder; LE, level of evidence

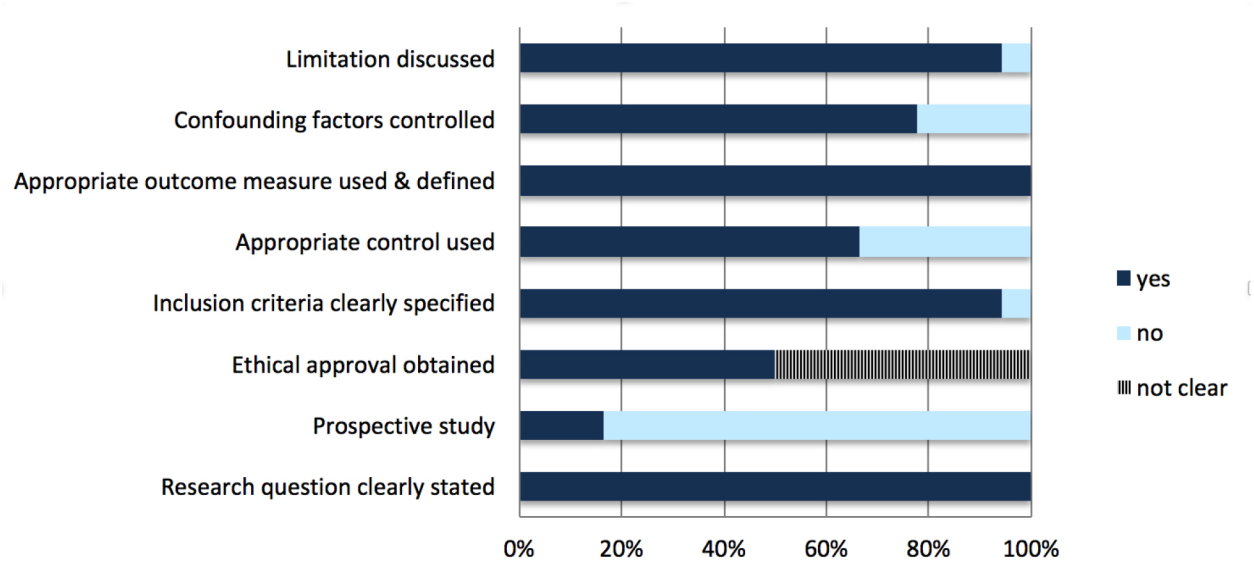

Figure 4-2. Methodological quality of the included studies

4.4.3 Outcome Measures

Across the included studies, over 20 kinds of outcome measures were used to evaluate the speech, reading, and auditory performances in order to assess the impact of the GJB2 mutation status after CI. The most commonly used outcome measures were speech recognition (word and sentence) scores, Infant Toddler Meaningful Auditory Integration Scale (IT–MAIS), Categorized Auditory Performance (CAP), and Speech Intelligibility Rating (SIR).

Word Recognition Score: Word recognition scores were reported in 10 studies[9,86,89-91,93,95,96,101,102]. Different etiologies of hearing loss in non-GJB2-related patients in these studies were analyzed separately. Meta-analysis showed that the difference between GJB2-related deafness and non-GJB2-related deafness due to non-syndromic hearing loss of unknown origin was not statistically significant (total mean difference 9.15 [-3.27 to 21.57], P=0.15) (Figure 4-3A). The difference between GJB2-related deafness and acquired hearing loss due to environmental etiologies was statistically significant and favoured GJB2-related deafness (total

mean difference 16.39 [1.48 to 31.30], P=0.03) (Figure 4-3B). The difference between GJB2-related deafness and other types of genetic deafness without additional disabilities was not statistically significant (total mean difference -6.25 [-17.97 to 5.46], P=0.3) (Figure 4-3C).

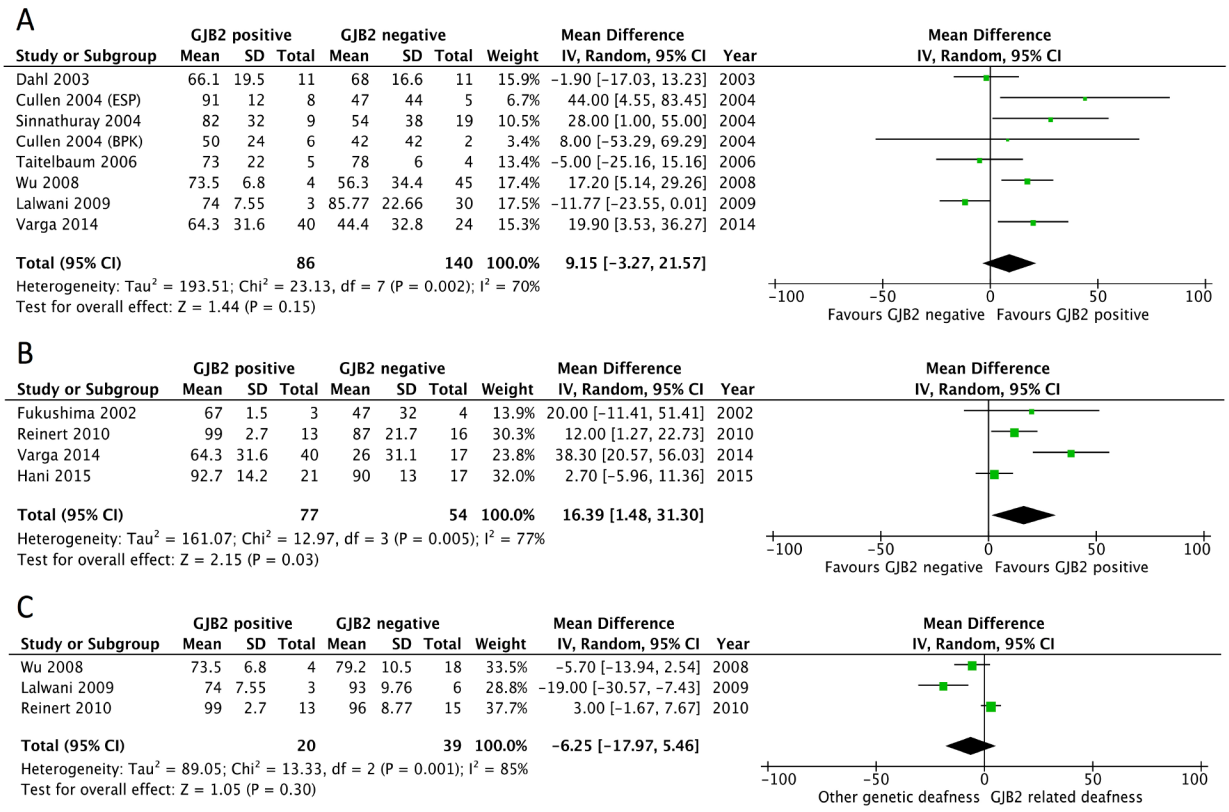

Figure 4-3. Word recognition score: (A) GJB2 related deafness vs. non-GJB2 related deafness due to non-syndromic hearing loss of unidentified origins; (B) GJB2 related deafness vs. acquired deafness; (C) GJB2 related deafness vs. genetic deafness besides GJB2 mutation.

Sentence Recognition Score: Sentence recognition scores were reported in 7 studies[91,93-97,102]. The pooled effect of sentence recognition scores in these 7 studies showed that although there was an obvious trend favoring GJB2 mutation, the difference between GJB2 positive and negative groups was not statistically significant (total mean difference 8.29 [-0.86 to 17.44], P=0.08)(Figure 4-4).

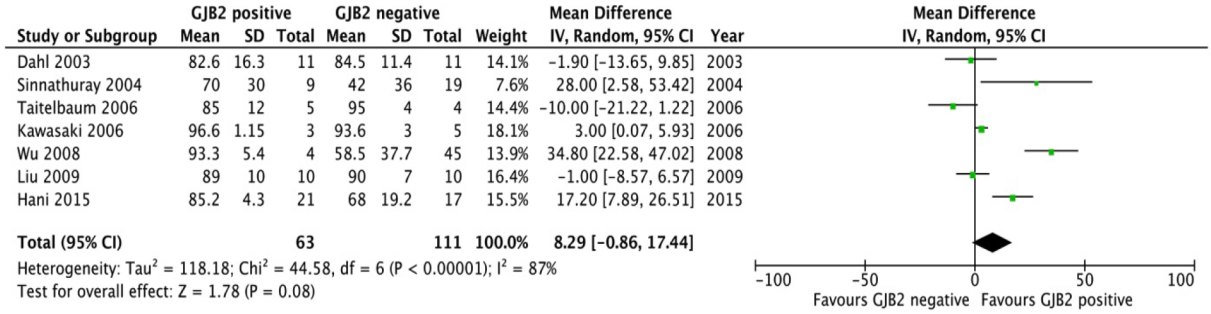

Figure 4-4. Sentence recognition score: GJB2 positive vs. GJB2 negative group

Infant Toddler Meaningful Auditory Integration Scale (IT -MAIS): IT-MAIS was reported in 5 studies[63,95,97,99,100]. The pooled effect of IT-MAIS showed that the difference between GJB2 positive and negative groups was not statistically significant (total mean difference 3.53 [-1.67 to 8.73], P=0.18)(Figure 4-5).

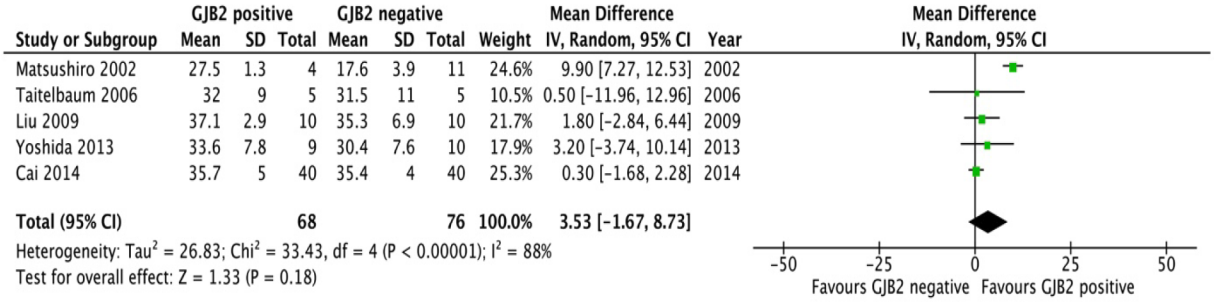

Figure 4-5. IT-MAIS: GJB2 positive vs. GJB2 negative group

Speech Intelligibility Rating (SIR): SIR was reported in 4 studies[92,97,98,100]. Meta-analysis showed that there was no statistically significant difference with respect to SIR between GJB2 positive and negative groups (total mean difference 0.16 [-0.29 to 0.61], P=0.48) (Figure 4-6).

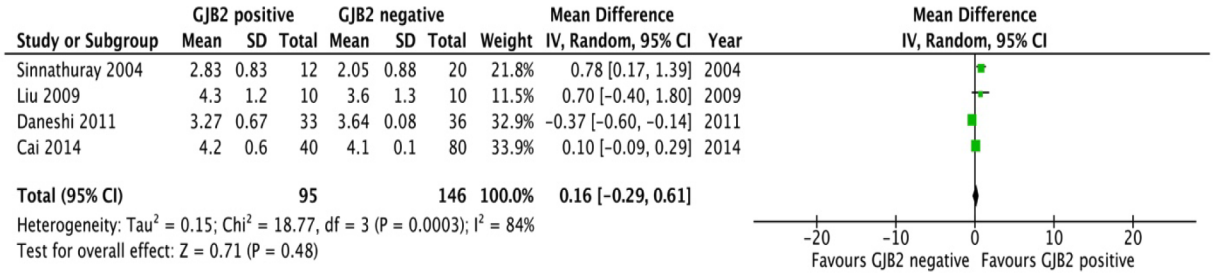

Figure 4-6. Speech intelligibility rating (SIR): GJB2 positive vs. GJB2 negative group

Categorized Auditory Performance (CAP): CAP was reported in 5 studies[10,97,98,100,101]. Meta-analysis showed that there was no statistically significant difference between GJB2 positive and negative groups in regard to CAP (total mean difference 0.08 [-0.21 to 0.37], p=0.6) (Figure 4-7).

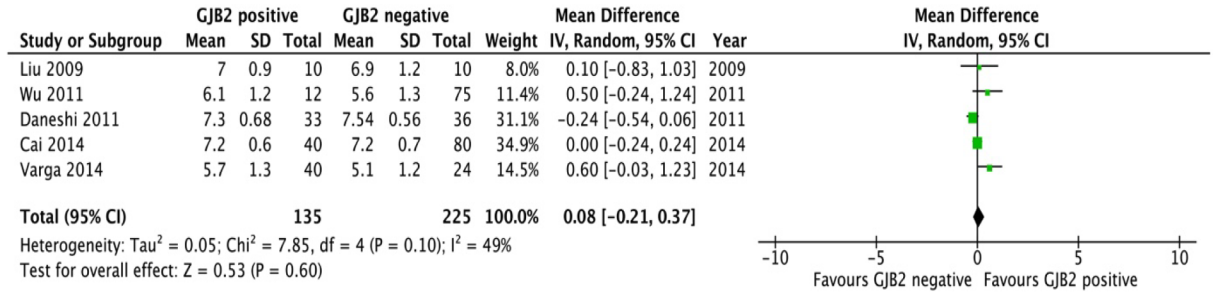

Figure 4-7. Categorized auditory performance (CAP): GJB2 positive vs. GJB2 negative group

4.5 Discussion

The effect of the GJB2 mutation status on the outcomes of pediatric cochlear implantation is controversial in numerous studies. In this quantitative research study, we analyzed the existing literature in order to assess the predictive value of the GJB2 mutation status on the outcomes of pediatric cochlear implantation (CI).

4.5.1 Word Recognition Outcomes

In the studies included for data synthesis of word recognition scores, deafness etiologies in non-GJB2-related patients vary among unidentified causes, genetic mutations besides GJB2 (mainly SLC26A4), and acquired environmental etiologies including prenatal (rubella, CMV infection), perinatal (prematurity, low birth weight), and postnatal causes (meningitis). To prevent the confounding effects of matching between the experimental (GJB2 mutation) and the control (non-GJB2 mutation) group on the pooling effect of the mutation status on CI outcome, we analyzed the GJB2 mutation versus these three types of etiologies separately. Results of meta-analysis showed that the difference in word recognition outcomes between GJB2-related deafness and non-GJB2-related deafness due to non-syndromic hearing loss of unknown etiology was not statistically significant. There was also no statistically significant difference between GJB2-related deafness and other types of genetic hearing loss without additional disabilities. However, GJB2-related deafness was associated with significantly better word recognition outcomes compared to acquired hearing loss due to environmental etiologies including low birth weight, prematurity, intrauterine infection, meningitis, CMV infection, and rubella.

4.5.2 Other Outcome Measures

With respect to sentence recognition scores and IT-MAIS, although there was a common trend favoring the GJB2 mutation group, the differences between the mutation and non-mutation groups did not reach statistical significance. With respect to SIR and CAP, there was no difference between GJB2-related deafness and non-GJB2-related deafness.

Our results indicated that GJB2-related deafness associates with significantly better CI outcomes when compared to acquired hearing loss due to environmental etiologies. This is because the latter is more frequently associated with deficits in higher brain and cognitive functions, such as semantic disorders, dyslexia, and dysgraphia; these deficits play a key negative role in proper language development after cochlear implantation[95]. However, if the control groups were matched carefully with respect to the factors that are known to affect language development and speech perception in children with impaired hearing such as age at implantation, etiology of hearing loss, and absence of co-morbidities, there is no significant advantage of harboring a GJB2 mutation over hearing loss of unknown etiologies or other types of genetic deafness with no additional disabilities. This finding supports the results of several individual studies[10,86,95,99]. Deafness etiology is unknown in about 40% of all investigated cases of pediatric deafness[103]. In these patients, hearing loss is the only abnormality and a majority of them may likely to be non-syndromic hearing loss of genetic origin, as testing for all the deafness genes is not routinely available, and "most importantly, the responsible gene for almost 50 mapped loci has yet to be identified, and there are undoubtedly more loci to be discovered"[95]. Consequently, among the many genetic mutations involved in non-syndromic hearing loss, mutations leaving the auditory nerve and central auditory pathway intact may demonstrate at least equal benefits from CI as GJB2-related deafness.

4.5.3 Reasons for Controversies in Literature

In some studies included in this systematic review[90,93,102], various etiologies in patients with non-GBJ2-related hearing loss were studied together and not sub-grouped according to the etiology of deafness. Non-syndromic deafness is accompanied by no additional abnormalities, whereas many cases of acquired deafness often coexist with other deficits that have a key impact on proper brain and language development. Comparing GJB2-related deafness versus the above two types of hearing loss yields different results. Clearly, grouping all the cases of non-GJB2-related deafness together as a "control group" will confound the results. We believe this is one of the main reasons for the controversial reports in the literature. Additionally, the non-uniformity in

molecular testing for a GJB2 mutation and the variance in the definition regarding to GJB2 positivity may also have contributed for these controversies. Because most patients who have a single allele mutation usually are carriers and the presence of a single pathogenic allele does not explain the cause of deafness[104], they may actually have other causes for their hearing loss, since carriers are more likely than non-carriers to develop hearing impairment in the presence of other genetic defects or environmental factors[104,105]. Biallelic GJB2 mutations, on the other hand, are generally less commonly accompanied by other causes. Therefore, CI outcomes in patients with a monoallelic GJB2 mutation which are more commonly accompanied by other genetic defects or environmental factors would have more pronounced effects than those with biallelic GJB2 mutation.

4.5.4 Limitations of Our Systematic Review and Implications for Future Studies

Numerous types of outcome measures were used in the studies included in this review, making it difficult to optimally compare them all. For the speech recognition category alone, at least seven different tools were used to evaluate CI outcomes (CNC, ESP, PBK, BKB, GASP, Hebrew AB, and Mandarin speech test). Time of assessment ranged from six months to nine years after implantation. In addition, the majority of the studies were retrospective and small in sample size. All these heterogeneities and limitations produce biases and confound the pooled effect of the impact of GJB2 mutation status on CI outcomes, and inevitably limit the level of evidence of our systematic review. Another limitation of this systematic review is that most studies compared other genetic mutations with GJB2 mutation without explicitly matching these specific genes. As a result, there were not enough data to compare GJB2 with specific deafness genes when we performed this meta-analysis, thus weakening our conclusion. Carefully controlled, prospective studies with a larger sample population and a similar reporting methodology would be necessary to provide more insight into the effect of a GJB2 mutation on the outcome of CI. Also, in future studies, it is important to compare GJB2 with specific deafness genes to determine the difference of CI outcomes between deafness of distinct etiology.

4.6 Conclusion

GJB2-related deafness correlates with significantly better CI outcomes when compared to acquired deafness caused by environmental etiologies, mainly because the latter is frequently associated with other deficits and co-morbidity. However, if patients are matched carefully with respect to factors such as age at implantation, etiology of hearing loss, and absence of co-morbidities, carrying the GJB2 mutation is not associated with a better prognosis when compared with those whose deafness results either from non-syndromic hearing loss of unknown origin, or other types of genetic mutations in the absence of other neurological deficits. This result suggests that it is not the presence or absence of a GJB2 mutation; rather, it is the accompanying health and neurologically related concerns that are critical for CI outcomes. This finding has important implications in counseling for cochlear implant candidates.

4.7 Linking Statement to the Next Chapter

Even with the best surgical conditions and genetic factors, cochlear implant (CI) recipients experience difficulties understanding speech in the presence of background noise or when several acoustic sources are present at the same time. The exact reason for this phenomena is poorly understood. In particular, it is not clear whether CI recepients are capable of perceiving auditory streaming (i.e. perceptually segregating the auditory scene into meaningful streams) and how they differ from normal hearing listeners in this capacity. The next chapter will continue to predict cochlear implantation outcomes by comparing auditory streaming segregation in CI recipients and normal hearing listeners.

CHAPTER FIVE: Auditory Streaming in Cochlear Implant Recipients (Manuscript 3)

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5.1 Introduction and Objectives

Auditory streaming (also referred to as auditory stream segregation) is the process used to separate a complex sound into different perceptual streams, often corresponding to the different individual sources from which the sound is derived. This kind of auditory process occurs naturally in daily life. When focusing on a speaker at a party or following the melody of a particular instrument in an orchestra, listeners with normal hearing interpret the mixture of sounds in such a way that sounds from different sources are allocated to individual sound generators. Cochlear implantation (CI) users and hearing impaired listeners, on the other hand, experience difficulties with speech understanding, or following a melody, in an environment having background noise, or when several acoustic sources are present at the same time. Reduced audibility probably accounts for these phenomena. However, these difficulties are not systematically alleviated even when the external signals are amplified to the listener's comfort level by means of hearing aids. This fact indicates that streaming difficulties cannot be explained by reduced audibility[106].

Early experiments by van Noorden and Bregman et al. demonstrated that certain conditions give rise to stream segregation[107,108]. When listeners were asked to describe how they perceived a repeating sequence of ABA tones, when A and B represent tones of a different frequency, it has been shown that when the frequency separation between the A and B tones is small, listeners perceive a single stream of a galloping A and B tone. However, when the frequency separation between the two tones increased beyond a certain limit, which known as the "fission / streaming threshold", the sequence gives rise to two separate perceptual streams formed by tone A and tone B. One possible explanation for this phenomena is that, "beyond this certain frequency separation limit, the two tones excite well-separated peripheral auditory filters, and these stimuli, which are conveyed by different auditory channels, can be assigned by the central auditory system to separate streams, whereas stimuli occupying the same or overlapping peripheral channel tend to be assigned to single stream"[109].

When a CI stimulates the auditory nerve electrically, the signal is picked up by an external microphone and is then mapped to a linear array of 12–22 independent electrodes which are inserted into the cochlea. Each of these electrodes covers a apecified frequency range. If stream segregation is based on frequency discrimination, the streaming ability of CI users should be worse than that of normal-hearing listeners due to the physiological and technical constraints and limited numbers of CI electrodes compared to human cochlea. It is well known that, although CI users generally understand speech well in quiet environments, they have difficulties understanding speech in the presence of background noise, or a competing speech.

In view of these issues, the objectives of this study are (i) to investigate whether CI users are capable of perceiving streaming segregation and (ii) to determine how they differ from normal hearing listeners.

5.2 Materials and Methods

5.2.1 Participants

26 CI users and 12 normal hearing controls participated in this study. Table 5-1 and 5-2 show the demographic data of each group. The study was approved by the CRIR(Centre de Recherche Interdisciplinaire en Réadaptation) ethics committee. Each participant provided written informed consent to take part in the study.

Table 5-1. Demographic data of normal hearing listeners

Subject	Age /Gender	Education level	Music education	Streaming threshold	AMT	Speech score/50
C01	29/F	6	violin	3	-9.67	50
C02	18/F	2	piano	3	-12.17	50
C03	22/F	4	piano	3	-9.33	50
C04	42/F	4	trompette		-8.83	50
C05	62/F	2	no	6	-6.83	50
C06	55/F	2	melodica	3	-10.17	50
C07	59/F	7	no		-11.83	50
C08	21/M	2	piano		-13.83	50
C09	52/F	7	no	4	-14.00	50
C10	40/M	4	violin	4	-15.00	50
C11	56/M	2	piano		-8.83	50
C12	20/F	2	piano	4	-16.67	50

Education level: 1: Secondary; 2:Cegep; 3:DEP; 4:Bac; 5:Masters; 6: PhD. Streaming threshold was measured at at 8 semitones/s; AMT: amplitude modulation threshold.

Table 5-2. Demographic data of cochlear implanatation users

Subject	Age /Gender	CI Side	Education level	Music education	Streaming threshold	AMT	Speech score/50
S01	22/F		4	Piano	6	-13.67	33
S02	22/F	R	4	No		-1.50	31
S03	43/M	L	3	No		-2.67	
S04	51/F	R	3	No	4	-2.33	38
S05	19/F	R	2	Guitar		-12.33	36
S06	29/F	L	4	No	4	-1.83	
S07	63/F	L	5	No	3	-4.83	42
S08	23/M	R	3	No		-3.17	
S09	35/M	L	4	No	4	-6.50	
S10	49/F	R	5	Piano	3	-4.67	38
S11	56/F	R	2	No	3	-1.50	45
S12	33/F	R	5	Violin	3	-5.67	47
S13	53	B			3	-3.83	34
S14	43/M	B	1	No		0.12	
S15	65/M	R	4	No	7	0.12	28
S16	47/F	R	4	No		0.12	28
S17	51/F	L	1	No		-7.83	28
S18	41/F	L	5	No		-13.00	29
S19	57/F	B	3	No		-4.17	39
S20	43/F	R	3	No		0.12	19
S21	20/M	L	2	No		-7.83	18
S22	58/F	L	5	No		-2.67	45
S23	58/F	L	4	Batterie		-10.67	40
S24	54/M	R	5	No		-2.83	7
S25	52/M		1	No		-3.17	40

Education level: 1: Secondary; 2: Cegep; 3: DEP; 4: Bac; 5: Masters; 6: PhD. R: right side. L: left side. B: both sides. Streaming threshold was measured at at 8 semitones/s.

5.2.2 Auditory Stimuli

Stimuli The stimulus consisted of sound sequences continuously looped for a 36s period. The structure of the sequence alternated A and B tones in the form of AAAAB. The sounds were 85ms long, with 15ms rise and fall cosine ramps. An interstimulus interval (ISI) of 40ms was inserted between all tones, resulting in an stimulus onset asynchrony (SOA) of 125ms and a repetition rate of 8Hz. This sequence design allowed the neural responses elicited by the sound sequence itself to be distinguished from the responses specifically related to the pitch contrast between A and B tones, based on their distinct repetition rate (8 Hz corresponding to the base

frequency of the sequence of tones; 8 Hz/5 = 1.6 Hz corresponding to the frequency of occurrence of the oddball B tone). The f_0 of the A tone was always 1000 Hz.

Conditions There were three conditions, each with a different frequency separation (Δf) between A and B tones. In the first condition, Δf was equal to 40 cents (0.4 semitones). In the second condition, Δf was equal to 400 cents (4 semitones) and in the third condition, Δf was equal to 1400 cents (14 semitones). Based on previous work studying discrimination and streaming at different rates and pitch contrasts in CI users, the values of pitch contrast and presentation frequency of the sequences chosen here were expected to unambiguously yield no discrimination between A and B tones in condition 1, discrimination but not streaming between the two tones in condition 2 and discrimination and streaming in condition 3. This was confirmed subjectively by asking each subject at the end of each sequence to describe the tone discrimination and streaming that they had heard. As expected, each participant systematically reported discriminating A and B tones in conditions 2 and 3 and all participants reported a streaming effect in condition 3. Streaming was reported by the participants as 'a feeling that an additional, high-pitched, sound was played on top of a stream of quickly repeating low-pitched tones'.

5.2.3 Experimental Environment

Participants were comfortably seated in a chair with the back of the head resting on a support. They were instructed to relax, to avoid any unnecessary head or body movement and to keep their eyes fixated on a point displayed on a computer screen in front of them. Sound sequences from the three conditions were presented in separate blocks. In each block, the 36s auditory sequence was repeated 8 times. The onset of each pattern was self-paced and preceded by a 3s pre period. The order of the blocks was counter-balanced across participants. To help participants to focused their attention on the upcoming sound sequence, they were reminded to listen carefully to the sequence. At the end of each block, participants were asked to describe their what they had heard. Specifically, they were asked to report how many different tone pitches they had heard during the sequence and whether these tones were perceived as originating from a single or from two distinct sound sources. This terminology was used because

segregated auditory streams are usually associated with distinct sound sources (see van Noorden, 1975[107]; Bregman, 1990[108]).

5.2.4 Data Analysis

From the participants' responses, the proportions of perception as either one-stream or two-stream were calculated for each condition. In CI users, the correlation between streaming threshold and speech score, the correlation between AMT and speech score and the correlation between streaming threshold and AMT were calculated. In addition, an examination was made as to whether factors including age, level of education and formal music education affected streaming capability. Before estimating all correlations, sample distributions were tested to ensure that thay were not significantly different from jointly Gaussian distributions.

5.3 Results

5.3.1 Proportions of Perception Types

To assess whether listeners perceived one (single) stream or two (segregated) streams with the increase of the frequency separation (Δf) between the two tones, the proportions of percept for both normal hearing(NH) listeners and CI users were calculated for the three different conditions. Results showed that as Δf increased, the proportion of two-stream percepts tended to increase as well, in both NH listeners and CI users (Figure 5-1).

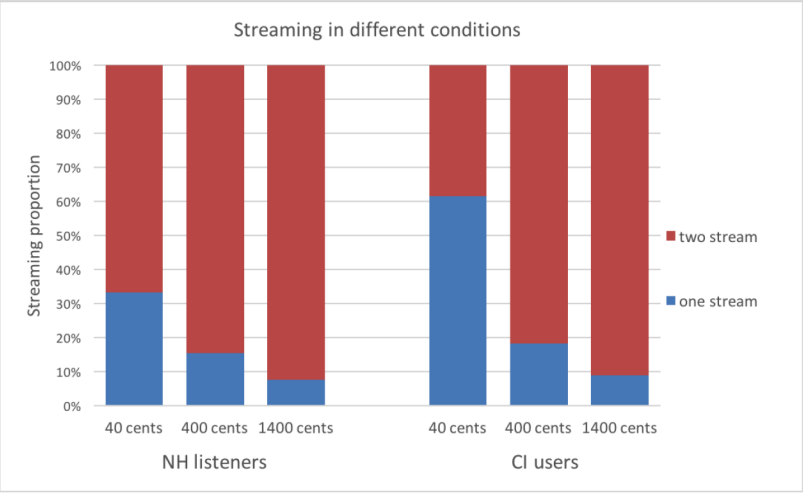

Figure 5-1. Proportions of streaming percept for different conditions in NH listeners and CI users

A X^2 test showed that NH listeners had significantly better streaming abilities when the frequency separation between two tones was 40 cents (P=0.04). However, when the frequency separation reached 400 cents or more, there was no significant streaming difference between NH listeners and CI users (P=0.48).

5.3.2 Streaming and Amplitude Modulation Threshold (AMT)

The streaming threshold and AMT in both CI users and NH listeners were summarized and compared with the aid of a box and whisker plot. Figure 5-2 shows that there was no significant difference in streaming threshold between NH listeners and CI users while the AMT was significantly lower in NH listeners than CI users (Figure 5-3).

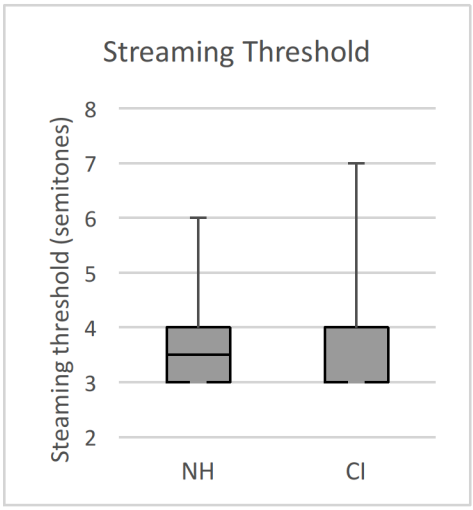

Figure 5-2. Streaming threshold: NH vs. CI users

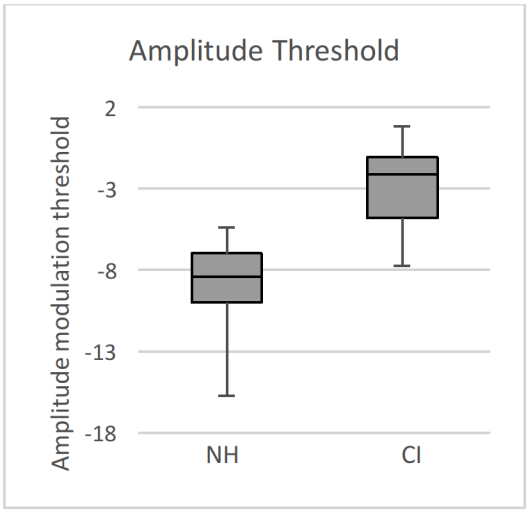

Figure 5-3. AMT: NH vs. CI users

5.3.3 Correlation

1. Speech score & AMT in CI users

No significant correlation was found between speech score and amplitude modulation threshold in CI users (correlation coefficient was -0.149, P=0.643) (Figure 5-4).

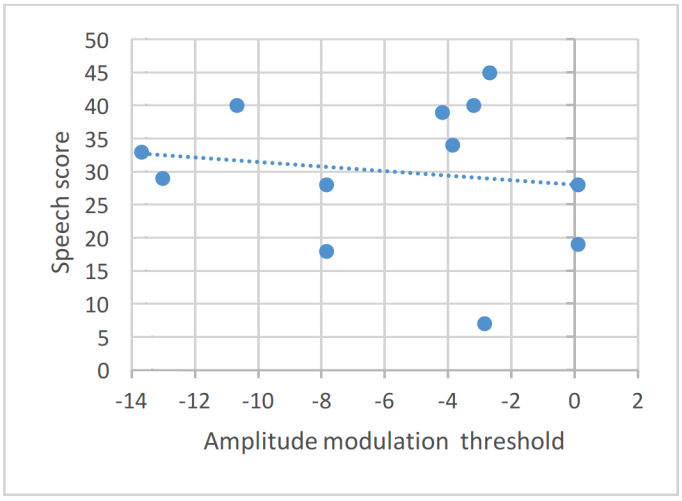

Figure 5-4. Correlation between Speech Score and AMT in CI users

2. Speech score & streaming threshold in CI users

A significant negative correlation was noted between speech score and streaming threshold in CI users (correlation coefficient was -0.779, P=0.023) (Figure 5-5).

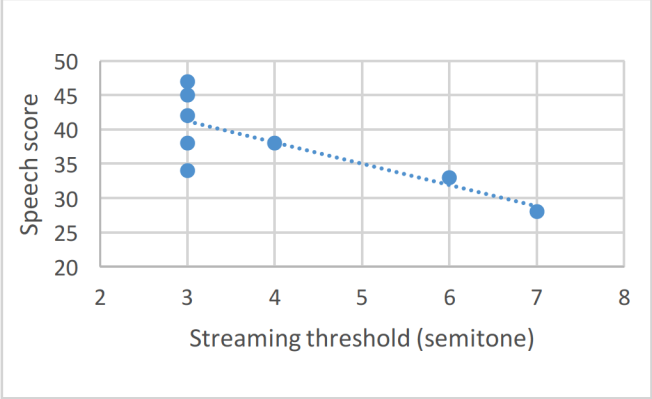

Figure 5-5. Correlation between Speech Score and streaming threshold in CI users

3. Streaming threshold & AMT in NH listeners

No significant correlation was found between the streaming threshold and AMT in NH listeners (correlation coefficient was 0.175, P=0.678) (Figure 5-6).

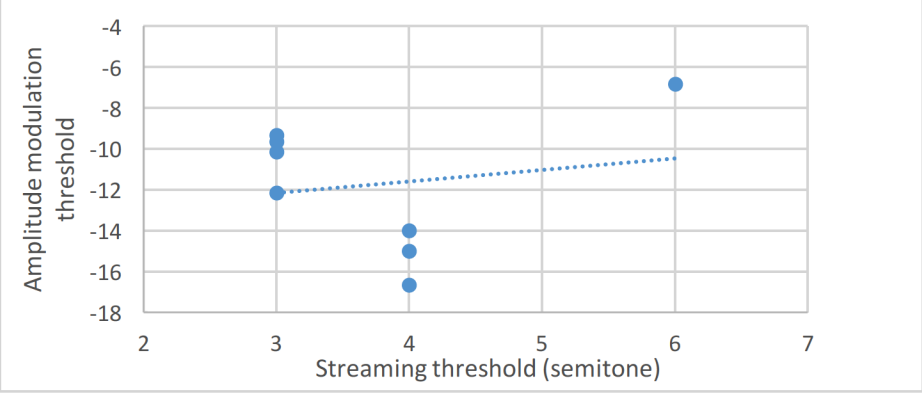

Figure 5-6. Correlation between Streaming threshold & AMT in NH listeners

4. Streaming threshold & AMT in CI users

No significant correlation was found between the streaming threshold & AMT in CI users (correlation coefficient was -0.135, P=0.729) (Figure 5-7).

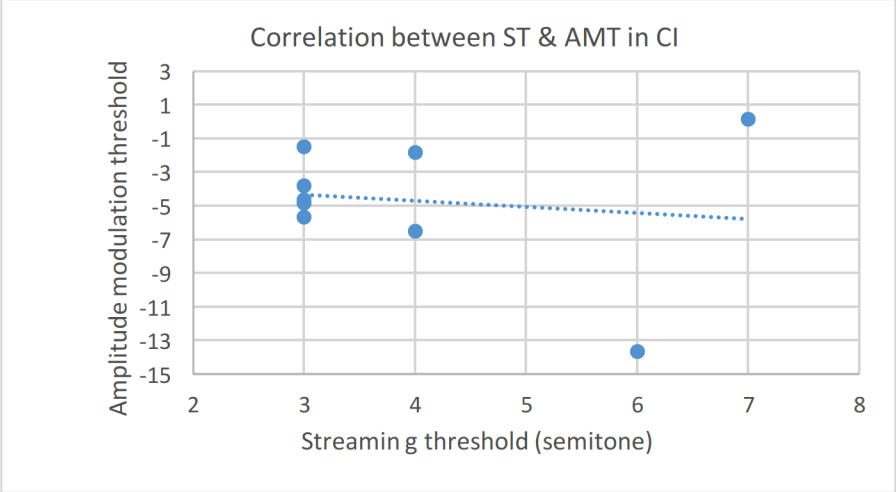

Figure 5-7. Correlation between Streaming threshold & AMT in CI users

5. Correlation between Streaming Threshold and patient Age

No significant correlation was found between patient age and streaming threshold for either NH listeners or CI users (correlation coefficient was -0.091, P=0.830) (Figure 5-8).

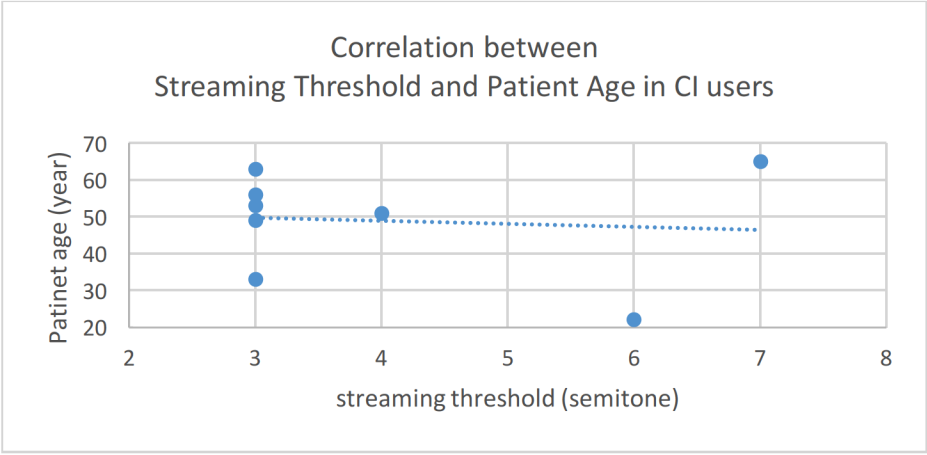

Figure 5-8. Correlation between streaming threshold and patient age

6. Correlation between level of education and streaming threshold

No significant correlation was found between level of education and streaming threshold for either CI users or NH listeners (correlation coefficient was -0.086, P=0.826) (Figure 5-9).

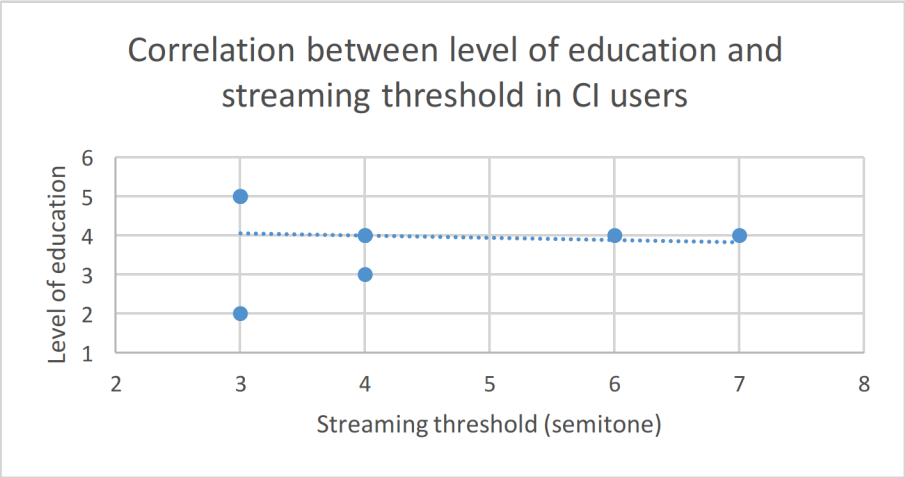

Figure 5-9. Correlation between level of education and streaming threshold in CI users

5.4 Discussion

5.4.1 Perceptual Segregation in CI Users

This study has demonstrated that when the frequency separation between the A and B harmonic complexes was small, CI users showed significantly less favorable streaming segregation ability than NH listeners. However, with an increased frequency separation, CI users showed an increasing tendency to have a two-stream percept, which is similar to that found with NH listeners. This finding supports the result of Böckmann-Barthel and his colleagues (2014) who reported that with an increasing frequency separation, the proportion assigned to a two-stream percept increased significantly and the proportion assigned to a one-stream percept decreased[110]. If the frequency separation between the two tones was high enough, the streaming difference between NH listeners and CI users was not significantly different. Our result also supports the "Peripheral Channeling" theory suggesting that streaming depends primarily on the amount of

overlap or separation in the excitation pattern on the basilar membrane induced by the two stimuli; the more the two stimulus excitation patterns overlap, the more likely they are to be perceived as a single stream, while the more the two stimulus excitation patterns separate, the more likely they are to be perceived as two separate streams.

5.4.2 Streaming Threshold and Speech Recognition in Noisy Backgrounds

Our hypothesis is that CI users who have difficulty streaming segregation will have more trouble understanding speech in environments with noisier backgrounds. Our results were consistent with this hypothesis. As expected, our results showed that a significant correlation existed between streaming threshold and speech recognition scores, which indicated that better auditory streaming capabilities correlated with better speech understanding. According to our results, better frequency resolution leads to improved auditory streaming, and better auditory streaming segregation leads to improved speech perception in noise. This result is consistent with findings in the literature that have suggested that frequency resolution and auditory streaming are important determinants in the ability to understand speech in noisy conditions[111].

5.4.3 Contributing Factors for Stream Segregation

Our results suggest that frequency resolution is a contributing factor for auditory streaming. However, other factors beyond the frequency resolution process are also likely to be involved in auditory stream segregation and speech perception in noise, such as a patient's hearing, age, level of education, and formal musical education.

Hearing Certain hearing impairments can affect basilar membrane mechanisms and can increase the region of excitation along the basilar membrane. Similarly, the spread of current in a cochlear implant (CI) causes the stimulation of a wider area around each electrode[112]. According to the "Peripheral Channeling" theory, the more the two stimulus excitation patterns overlap, the more likely they are to be perceived as a single stream; therefore, hearing impaired listeners should show a reduced ability with auditory streaming[112]. Also, some evidence showed that hearing impaired listeners associate with deficits in their streaming segregation abilities[113]. However,

these difficulties were not systematically alleviated even when the external signals were amplified to the listener's comfort level[106]. This fact indicates that reduced audibility may only partly account for streaming difficulties. In this study, we do not have enough data on pure tone audiometry results. However, speech recognition score significantly correlated with auditory streaming.

Patient age There was some evidence that age played a role in the streaming process, with poorer streaming performance being correlated with higher age in both normal-hearing and hearing-impaired groups[114]. In our study, CI users were older than normal hearing controls (median 52 vs. 36 years, mean 49 vs. 37 years). Thus, it can be argued that the comparison was confounded by age. In agreement with this hypothesis, Rose and Moore et al.[115] found an increased streaming threshold in some but not all hearing-impaired listeners. In their study, the increased fission boundaries could not be explained completely by the age of the patients. When controlling for the hearing loss, Snyder and Alain et al. found that no effect could be attributed to age in sequential stream segregation[116]. Furthermore, there was little evidence for a deterioration of a general CI performance with increasing age. Our results also demonstrated that there was no significant correlation between streaming threshold and age of CI users. Therefore, age appeared to have no effect on auditory streaming.

Level of education and formal musical education Our results showed that there was no correlation between the level of education and streaming threshold. Also, there was no correlation between formal musical education and streaming threshold.

5.5 Conclusion

The present study provides evidence that most CI users show stream segregation that was very similar to normal-hearing listeners. With increasing frequency separation, CI users showed a steady increase of their streaming percept, which was similar to that found in NH listeners. This similarity suggests that the quality of stream formation was not altered when the auditory input

was provided via a CI. Patient age and level of musical education had little effect on auditory streaming.

Further research should address the relationship between auditory streaming capability, speech in noisy environments, and other factors such as spread of excitation. This should yield better cochlear implantation outcomes and should permit earlier interventions.

CHAPTER SIX: Summary

6.1 General Discussion

Cochlear implantation (CI) has become an established and routine treatment to improve hearing in profoundly deaf patients. Currently, more children are receiving CI than adults world wide[44]. The outcomes of CI have improved significantly over the past two decades, mainly because of technical improvements such as the refinement of electrode designs and speech-processing strategies. Language performance after CI is highly variable and depends on many factors. Since cochlear implantation is an expensive and invasive procedure, prediction of CI outcome is very important for judicious candidate confirmation. This thesis has focussed on the prediction of CI outcomes in different patient populations, specifically (i) in patients with advanced otosclerosis, (ii) in children with GJB2 mutation, and (iii)in the streaming abilities of CI recipients.

Chapter 1 presented the rationale and objectives of the thesis. Chapter 2 provided an overview of the history of CI and a review of relevant literature, emphasizing the evolution of CI candidacy and prognostic factors for outcomes of pediatric CI.

Chapter 3 focused on the efficacy and value of CI for the management of profound deafness in patients with advanced otosclerosis. However, in the last decade, there have been increasing numbers of studies investigating the efficacy of CI in cases of advanced otosclerosis, which were formerly candidates for hearing aids and stapedotomy. Two treatment approaches were compared and debated in the literature. A meta-analysis showed that CI leads to a statistically greater and consistent improvement in speech discrimination scores when compared to stapedotomy. However, stapedotomy is not universally effective: it yields results comparable to CI in half of the patients. For cases of unsuccessful stapedotomy, the option of CI is still open and the results obtained by a salvage CI are as good as those of a primary CI.

Chapter 4 evaluated the predictive value of GJB2 mutation status for auditory and speech performance in a pediatric CI population. The association of a GJB2 mutation with the outcomes of pediatric CI has been investigated extensively. Since the underlying pathology of a GJB2 mutation is related to cochlea hair cell dysfunction, which can be bypassed by CI, language outcomes in GJB2-related deafness are expected to be better than those in non-GJB2-related deafness. However, a controversy exists in the literature regarding better auditory and speech performance in cochlear implanted children with GJB2-related deafness. Our study indicated that GJB2-related deafness was associated with significantly better CI outcomes when compared to an acquired hearing loss due to environmental etiologies; it is because the latter is more frequently associated with deficits in higher brain and cognitive functions which play a key negative role in proper language development. However, if the control groups were matched carefully with respect to the factors that are known to affect language development, such as age at implantation, etiology of hearing loss and absence of co-morbidities, there was no significant advantage of harboring a GJB2 mutation over hearing loss of unknown etiologies or other types of genetic deafness with no additional disabilities.

Chapter 5 investigated whether CI users were capable of perceiving auditory stream segregation and compared how they differed from normal hearing listeners. It is well known that although CI users understand speech well in quiet environments, they experience difficulties in understanding speech in noisy environments. The experiment presented showed that when the frequency separation between A and B harmonic complexes was small, CI users exhibited significantly less favorable streaming abilities than normal hearing (NH) listeners. However, with increasing frequency separation, CI users showed a steady increase in the two-stream percept in the same way as normal hearing controls. This finding provides evidence that most CI users show the same stream segregation as normal-hearing listeners. This similarity of an increase of the frequency separation in CI users and the same steady increase of the streaming percept as normal hearing controls indicates that the quality of streaming formation is not altered when the auditory

input is provided via a CI. Also as expected, the results showed a significant correlation between streaming threshold and speech recognition scores, which indicates that improved auditory streaming correlates with improved speech understanding.

6.2 Overall Conclusion

(1) For patients of advanced otosclerosis, CI leads to statistically better and more consistent speech discrimination scores than stapedotomy.

(2) GJB2-related deafness is associated with significantly better CI outcomes when compared to an acquired hearing loss due to environmental etiologies. However, if the factors that affect language development are accounted for, there is no significant advantage of harboring a GJB2 mutation over a hearing loss of unknown etiologies or other types of genetic deafness with the absence of other disabilities.

(3) Most CI users show the same stream segregation capabilities as normal-hearing listeners. Thus,the quality of streaming formation is not altered when the auditory input is provided via a CI.

6.3 Suggestions for Future Research

(1) The systematic reviews presented in Chapters 3 and 4 were limited by the quantity and quality of the available literature. The heterogenities between studies, as well as the retrospective nature and small sample sizes, limitted the level of evidence provided by the meta-analysis. Thus there is a need for better controlled, prospective studies having larger sample populations, and employing similar reporting methodologies.

(2) Further research should address (a) the relationship between auditory streaming capabilities, speech in noisy environments, and (b) the influence of other lower-level parameters (such as spread of excitation), in order to better predict cochlear implantation outcomes and in order to better advise when earlier interventions would be beneficial.

CHAPTER SEVEN: References

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