RELATIONSHIP BETWEEN SENSORINEURAL HEARING LOSS AND VESTIBULAR AND BALANCE FUNCTION IN CHILDREN

By

Sharon Lynn Cushing

A thesis submitted in conformity with the requirement for the degree of Masters of Science

Graduate Department of the Institute of Medical Sciences

University of Toronto

© Copyright by Sharon Lynn Cushing 2008
ABSTRACT

Relationship between sensorineural hearing loss and vestibular and balance function in children

Masters of Science 2008

Sharon Lynn Cushing,

Institute of Medical Science, University of Toronto.

Similarities between the peripheral auditory and vestibular systems suggest that children with sensorineural hearing loss (SNHL) may demonstrate vestibular and balance impairments. This hypothesis was studied in 40 children with severe to profound SNHL and unilateral cochlear implants (CI). Vestibular function was assessed with caloric, rotational, and vestibular evoked myogenic potential (VEMP) testing; balance was assessed with standardized static and dynamic tests. Horizontal semicircular canal function was abnormal in 53% (17/32) with caloric, and 39% (14/36) with rotational stimulation. Saccular function was absent bilaterally in 5/26 (19%) and unilaterally in 5/26 (19%) with VEMP. Balance abilities were significantly poorer (μ=12.9±5(SD)) than normal hearing controls (μ=17±5(SD); p=0.0006) and correlated best with horizontal canal function from rotational stimulation (p=0.004;R²=0.24). SNHL from meningitis was associated with worse balance function than other etiologies. Vestibular and balance dysfunction occurred in >1/3 of children with SNHL and CI, and is highly dependent on etiology.
ACKNOWLEDGEMENTS

An incredible number of individuals were involved in the success and completion of this project and I extend sincere thanks to all of them with special thanks to:

MY RESEARCH SUPERVISORS, Drs. Karen Gordon and Robert Harrison for providing me with the foundation, imparting your expertise and guiding me through this process, I am truly grateful for your tireless dedication.

MY CLINICAL SUPERVISORS, Drs. Blake Papsin, John Rutka and Adrian James for enabling this project, providing limitless time and encouragement and ultimately setting me up to succeed, you are the ultimate in mentors and role models. Thanks also to Dr. Neil Baillie for the assistance with clinical testing and manuscript preparation.

MY COMMITTEE, Drs. Karen Gordon, Robert Harrison and Diane Broussard for your time, advice and recommendations which were invaluable to the project and its completion.

THE COCHLEAR IMPLANT LAB and TO THE COMMUNICATIONS DEPARTMENT, Patt, Diane, Jerome, Claire, Stefanie, Vicky, Laurie, Marylynn, Ruth, Gina and Pat for your help encouragement and friendship, you have made this such a fun ride.

THE HEARING AND BALANCE UNIT – TORONTO GENERAL HOSPITAL: Heather, Al, Julie, Wanda, Eileen, Barb, Melissa, and Georgette for your enthusiasm, diligence and willingness in taking on the challenge of testing these children, you truly went above and beyond.

MY FAMILY: My husband, Dean for allowing me to take on this challenge, follow my dreams and do what I love. My dad, Richard for being my ever-ready and willing advisor. My mom, Alicia for your love and prayers, I can hardly imagine the number of candles that have gone up in smoke on my account. My sister, Karen for being the ultimate sounding board.
CHAPTER 1: INTRODUCTION ........................................................................................................ 1
1.1 RESEARCH QUESTIONS ........................................................................................................... 1
1.2 BACKGROUND ....................................................................................................................... 2
1.3 ANATOMY AND PHYSIOLOGY OF THE PERIPHERAL VESTIBULAR SYSTEM .................... 3
1.4 TESTS OF VESTIBULAR END ORGAN FUNCTION .................................................................. 6
1.5 ANATOMIC AND FUNCTIONAL DEVELOPMENT OF THE INNER EAR ...................... 9
1.6 RELIABILITY AND LIMITS OF TESTING VESTIBULAR AND BALANCE FUNCTION IN CHILDREN 11
1.7 RELATIONSHIP BETWEEN SENSORINEURAL HEARING LOSS AND VESTIBULAR FUNCTION .... 13
  1.7.1 Incidence of vestibular lesions amongst those with cochlear lesions ......................... 14
  1.7.2 Etiologic differences and the combined audiovestibular loss ..................................... 14
  1.7.3 Relationship between hearing thresholds and vestibular function ............................ 16
  1.7.4 Relationship between tests of vestibular end organ function and balance in the setting of SNHL .............................................................. 17
1.8 IMPLANTATION AND VESTIBULAR FUNCTION .................................................................. 22
1.9 SUMMARY ............................................................................................................................ 27

CHAPTER 2: METHODS ................................................................................................................. 28
2.1 SUBJECTS .............................................................................................................................. 28
2.2 ASSESSMENT OF HORIZONTAL SEMICIRCULAR CANAL FUNCTION ............................. 29
  2.2.1 Caloric stimulus .............................................................................................................. 29
  2.2.2 Rotational chair testing ................................................................................................. 31
2.3 ASSESSMENT OF SACCULAR FUNCTION ......................................................................... 32
2.4 STATIC AND DYNAMIC BALANCE TESTING .................................................................... 33
2.5 CLINICAL TESTS OF VESTIBULAR FUNCTION ................................................................ 33
2.6 TEMPORAL BONE IMAGING .............................................................................................. 34
2.7 MOLECULAR GENETIC EVALUATION ................................................................................. 34
2.8 DATA AND ANALYSIS .......................................................................................................... 35
  2.8.1 Tests of vestibular end organ function ......................................................................... 35
  2.8.2 Clinical neuro-otologic testing ...................................................................................... 35
  2.8.3 Static and dynamic balance .......................................................................................... 36

CHAPTER 3: RESULTS .................................................................................................................. 37
3.1 COMPLIANCE WITH TESTING .............................................................................................. 38
3.2 HORIZONTAL SEMICIRCULAR CANAL FUNCTION .......................................................... 39
  3.2.1 Caloric stimulation ........................................................................................................ 39
  3.2.2 Rotational chair testing ................................................................................................. 39
3.3 SACCULAR FUNCTION .......................................................................................................... 40
# List of Tables

1.1 Bruininks-Oseretsky Test of Motor Proficiency 2 Balance Subtest Items and Grading Scheme ........................................ 20  
2.1 Etiology and Onset of SNHL in Study Population .................. 28  
2.2 Standard Battery of Clinical Neuro-Otologic Tests and Function Tested ................................................................. 33  
3.1 One-Way Analysis of Variance Testing the Effect of Etiology on Performance on the BOT-2 ................................. 44  
3.2 Analysis of Rotational Chair Test Results as a Categorical vs. Continuous Variable Predictor of BOT-2 Score .................. 46  
3.3 Predictive Ability of the Mean VOR Gain in Light and Dark for BOT-2 Score at Low and High Frequencies .................... 47  
3.4 Univariate Linear Regression Analysis of Factors Influencing Standardized Score on Balance Subset of BOT-2 .................. 48  
3.5 Multivariate Analysis with 3 Separate Tests of Lateral Canal Function as Main Predictor Variables ................................. 53  
3.6 Best Fit Linear Regression Model .................................................. 53  
3.7 Paired T-Test for Mean VOR Gain in Non-Implanted Ear vs. Implanted Ear Across Frequencies in Light and in Dark ........ 55  
3.8 Difference of Mean VOR Gain in Light vs. Dark ....................... 57  
3.9 Difference of Mean VOR Gain in Light vs. Dark for Subjects with Categorically Abnormal Rotational Test Results ............ 59  
3.10 Repeated Measures ANOVA Examining the Impact of Vision on One Item of the BOT-2 in Subjects with Abnormal Rotational Chair Testing ................................................................. 61  
3.11 Repeated Measures ANOVA Examining the Impact of Vision on One Item of the BOT-2 ................................................................. 63  
A.1. Individual Study Subject Data .................................................. 105
### LIST OF FIGURES

1.1 COCHLEA AND VESTIBULAR END ORGANS ........................................ 3
1.2 CONFIGURATION OF THE CUPULA AND CRISTA WITHIN THE AMPULATED END OF THE SEMICIRCULAR CANAL .......................... 4
1.3 MORPHOLOGICAL POLARIZATIONS OF THE STEREOCILIARY BUNDLES IN THE MACULAE OF THE SACCULE AND UTRICLE .......... 5
1.4 THE VESTIBULOOCULAR REFLEX PATHWAY ........................................... 6
1.5 THE VESTIBULOCOLLIC REFLEX PATHWAY ........................................... 7
1.6 RELATIVE PLACEMENT OF COCHLEAR IMPLANT COMPONENTS ............ 23
2.1 ENG EYE POSITION RECORDINGS .................................................. 30
2.2 VESTIBULAR EVOKED MYOGENIC POTENTIAL ..................................... 32
3.1 VOR GAIN ACROSS FREQUENCY OF SINUSOIDAL ROTATION IN DARK .............................................................................. 40
3.2 AGE STANDARDIZED SCORE ON BALANCE SUBSET OF BOT-2 AGAINST RESULTS OF VESTIBULAR END ORGAN TESTING ......................... 45
3.3 AGE STANDARDIZED SCORE ON BALANCE SUBSET OF BOT-2 BY AGE AT IMPLANTATION AND DURATION OF IMPLANT USE ......................... 49
3.4 AGE STANDARDIZED SCORE ON BALANCE SUBSET OF BOT-2 BY ETIOLOGY AND TYPE OF HEARING LOSS) ................................. 50
3.5 AGE STANDARDIZED SCORE ON BALANCE SUBSET OF BOT-2 BY MEAN VOR GAIN IN LIGHT AND DARK SEPARATED BY FREQUENCIES (ALL, ≤2HZ, > 2HZ) ........................................................................ 58
3.6 AGE STANDARDIZED SCORE ON BALANCE SUBSET OF BOT-2 BY MEAN VOR GAIN IN LIGHT AND DARK SEPARATED BY FREQUENCIES (ALL, ≤2HZ, > 2HZ) FOR CHILDREN WITH ABNORMALITIES ON ROTATIONAL CHAIR TESTING ....................................................... 60
3.7 DURATION OF POSTURE MAINTENANCE WITH EYES OPENED AND CLOSED WITH AND WITHOUT A BALANCE BEAM FOR CHILDREN WITH PROFOUND SNHL AND UNILATERAL CI AND CHILDREN WITH SNHL, UNILATERAL CI AND ABNORMAL VOR ON ROTATIONAL
CHAIR TESTING .............................................................................................................. 62

3.8 COMPUTED TOMOGRAPHY OF A NORMAL TEMPORAL BONE ......................... 64

3.9 COMPUTED TOMOGRAPHY OF A TEMPORAL BONE IN A CHILD WITH ACQUIRED MENINGITIS ........................................................................................................... 65

3.10 5 YEAR FOLLOW-UP COMPUTED TOMOGRAPHY OF RIGHT TEMPORAL BONE IN A CHILD WITH ACQUIRED MENINGITIS ......................................................... 66

3.11 COMPUTED TOMOGRAPHY OF THE TEMPORAL BONE IN A CHILD WITH PROGRESSIVE HEARING LOSS OF UNKNOWN ETIOLOGY AND UNILATERAL LABYRINTHINE OSSIFICATION ......................................................... 67

3.12 COMPUTED TOMOGRAPHY OF THE TEMPORAL BONE OF A CHILD WITH FEATURES OF CHARGE ASSOCIATION ................................................................. 68

A.1. GRAPHICAL REPRESENTATION OF VESTIBULAR END-ORGAN (DYS)FUNCTION AS MEASURED BY CALORIC, ROTATIONAL AND VEMP TESTING. RESULTS ARE CATEGORIZED BY ETIOLOGY OF SNHL .......... 108
LIST OF APPENDICES

A.1 TABLE A.1. INDIVIDUAL STUDY SUBJECT DATA ........................................ 105

A.2 SUMMARY (LONG ABSTRACT) ................................................................. 106

A.3 FIGURE A.1. GRAPHICAL REPRESENTATION OF VESTIBULAR END-ORGAN
(DYS)FUNCTION AS MEASURED BY CALORIC, ROTATIONAL AND VEMP
TESTING. ........................................................................................................ 108

"THE VESTIBULAR OLYMPICS : A TEST OF DYNAMIC BALANCE
FUNCTION IN CHILDREN WITH COCHLEAR IMPLANTS." ARCH
OTORHINOLARYNGOL 134.(1): 34-38......................................................... 109
LIST OF ABBREVIATIONS

BOT2 – Bruininsk-Oseretsky test of motor proficiency 2
CI – cochlear implant
CT – computed tomography
DVA – Dynamic visual acuity
ENG – electronystagmography
MRI – magnetic resonance imaging
PTA – Pure tone average
SCM – Sternocleidomastoid muscle
SNHL – Sensorineural hearing loss
SSC – Semicircular canals
VEMP – Vestibular evoked myogenic potential
VOR – Vestibulo-ocular reflex
CHAPTER 1: INTRODUCTION

1.1 Research Questions

It has been well established that the relationship between auditory and vestibular (dys)function is complex. In the following body of work we will aim to answer the following questions:

1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?
2. What influence does etiology and the onset of deafness have on this relationship?
3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?
4. Does cochlear implantation alter vestibular end organ function?

Drawing appropriate conclusions about the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function requires an adequate understanding and control of the variables that influence this relationship. The literature suggests that these variables include at a minimum, hearing threshold and etiology of deafness. The current study aims to control for hearing threshold by including only children who are candidates for cochlear implantation. This represents a relatively homogeneous group given that candidacy for implantation requires hearing thresholds in the severe to profound range. Controlling for etiology is however a more challenging task given the large variety of inner ear injuries that lead to deafness. Our ability to identify the etiology of deafness has certainly increased with the advent of improved imaging and molecular genetic techniques. The current study will take advantage of these in classifying the study patients into etiologic categories. Despite these advancements, the etiology still is not identified in a significant proportion of children with SNHL and to reflect this reality, the current study will also include a heterogeneous subgroup of children in whom the etiology of deafness is unknown. Given the variability and challenges of testing pediatric patients, a combination of overlapping clinical and adjunctive tests will be conducted in order to reliably establish peripheral vestibular function in these children. The results of vestibular end organ testing will then be correlated with a test of dynamic and static
balance in an effort to establish the functional significance of any peripheral vestibular deficits. Through careful measures of peripheral vestibular and balance function in children with SNHL and acknowledgment and control of the heterogeneity within our study population of children with SNHL, we aim to clarify the relationship between auditory and vestibular end organ and balance function in children. We hypothesize that some children with auditory dysfunction (i.e. SNHL) may also demonstrate concurrent abnormalities of vestibular end organ function and that likely this relationship will depend on the nature and characteristics of the underlying insult or injury to the inner ear (i.e. etiology of deafness). We also expect that peripheral vestibular dysfunction will translate into abnormalities of static and dynamic balance. Finally, we expect that the insertion of a cochlear implant has the potential to disrupt the function of the vestibular end organs and that indeed this may be evident on follow-up tests of vestibular end organ function following implantation. However, given its cross sectional nature, the current study is not designed to answer the question of what the implication of such iatrogenic injuries may be on static and dynamic balance.

1.2 Background

The cochlea shares both an anatomic proximity, histologic and physiologic similarities to the neighbouring vestibular end organs. In both systems, the sensory epithelium is comprised of hair cells which are mechanoreceptors whose stereocilia are embedded in an overlying layer that provides an inertial mass. Differences between the systems exist only in the nature of the overlying layer (i.e. basilar membrane vs. otoconia etc.), the organization of the hair cells within the sensory epithelium (Organ of Corti vs. macula vs. cupula etc) and the mechanical stimulus that leads to movement of the inertial mass overlying the hair cells. In the context of the stimulus to which the end organ is tuned, movement of this inertial mass then translates into small deflections of the stereocilia and leads to changes in the activity of the primary afferents. For example, the mechanical stimulus would be sound in the setting of the cochlea and head rotation in the setting of the semicircular canals. It is therefore reasonable to theorize that in some instances, lesions or insults that lead to auditory dysfunction may also lead to dysfunction of the vestibular end organs. In turn, dysfunction of the vestibular end organs may cause disruption in the ability to maintain static and dynamic balance.
In order to properly assess the relationship between auditory, vestibular end organ and subsequently balance function in children, several factors must be considered.

1) Reliable and accurate methods of measuring auditory, vestibular end organ and balance function must be available.

2) The chosen method(s) of measuring vestibular end organ function should correlate with measures of balance function.

3) The nature, degree and time course of the most common cochlear/auditory insults need to be identified and sufficiently understood in order to draw parallels to the potential for concurrent vestibular end organ dysfunction.

However, addressing the above issues first requires a basic understanding of the anatomy and physiology of the peripheral vestibular system and this foundation will be provided in the following section.

1.3 Anatomy and physiology of the peripheral vestibular system

![Cochlea and vestibular end organs](image)

**Figure 1.1.** Cochlea and vestibular end organs. (From Brodel 1936)
All head and body movements can be broken down into a combination of angular and linear accelerations. The peripheral vestibular apparatus consists of two groups of sensory end organs: the three semicircular canals (SCC) and the two otolith organs (Figure 1.1) that are specialized to respectively respond to angular and linear acceleration respectively. Three pairs of SCCs (horizontal, superior and posterior) are found within the labyrinth on each side of the head, with each canal positioned at right angles to the others. Each of the SCC have an ampulated end and a non-ampulated end. The ampulated end of the SCC’s houses the cristae ampullaris upon which the hair cells are organized and the gelatinous cupula which provides the inertial mass overlying the hair cells and within which their stereocilia are embedded (Figure 1.2). The SCCs respond to angular head rotation within the plane of the canal. More specifically, changes in head position leads to movement of fluid within the paired SCC causing deflection of the cupula overlying the hair cells. Bending of the hair cell stereocilia leads to either hypo or hyperpolarization and inhibition or excitation of the primary afferents.

**Figure 1.2.** A. Configuration of the cupula and crista within the ampulated end of the semicircular. B. Cupular deflection in response to endolymph flow that is opposite in direction to head acceleration (large arrow). (From Carey and Della Santina 2005)
In comparison, the otolith organs lie within the vestibule and are responsible for sensing gravity and responding to linear acceleration. There are two otolith organs, the utricle and the saccule which lie at right angles to each other. Within each of the otoliths is housed a macula, which is a flat ovoid structure covered with hair cells across its surface. The stereocilia of these hair cells are embedded in the otoconia, a gelatinous overlying membrane that is weighted with calcium carbonate crystals. The sensitivity of the otolith organs to detecting translational acceleration is greatest when movement occurs in the plane of the maculae. Therefore, given their position, the utricle is sensitive to acceleration in the horizontal plane and the saccule is sensitive in the sagittal plane (Figure 1.3). Two primary pathways provide connectivity to and from the labyrinth; the vestibulo-ocular and the vestibulocollic and vestibulospinal pathways. The vestibuloocular reflex is the most well studied vestibular reflex. Specifically there are two

**Figure 1.3** Morphological polarizations of the stereociliary bundles in the maculae of the saccule and utricle. (Adapted from (Fluur and Mellstrom 1971))

types of vestibuloocular reflexes: 1) compensatory reflexes that stabilize gaze during motion (i.e. turning the head to the right 20 degrees leads to eye movements 20 degrees to the left) allowing for clarity of vision and 2) orienting reflexes that align the eyes with the gravitational vector. Figure 1.4 displays the three neuron arc that is responsible for the VOR. In the current study, assessment of the VOR will primarily focus on the gain of this reflex. Specifically, the
VOR gain is equal to the ratio of the magnitude of the compensatory eye movement over the magnitude of the head movement or body movement when the head is fixed.

Figure 1.4. The Vestibuloocular Reflex Pathway. (From Brown 2005)

The primary function of the vestibulocollic and vestibulo-spinal pathways is to stabilize the head and body and maintain it upright against the force of gravity and, together with the VOR, to help stabilize gaze and the body while walking and running (Cohen and Raphan 2004). Figure 1.5 displays the details of the pathway responsible for the vestibulocollic reflex. Following from this brief overview of the anatomy and physiology of the vestibular end organs and peripheral vestibular pathways, we will now focus on the methods for assessing both the integrity and function of the peripheral vestibular system.

1.4 Tests of vestibular end organ function

Ideally, a single test would probe the overall function of the peripheral vestibular system, isolate individual end organ function, and test the integrity of the peripheral pathways. Unfortunately, the available tests of vestibular end organ function are much more limited. The majority of clinical tests of the peripheral vestibular system reflect the function of the horizontal
Semicircular canal and this end organ is most commonly assessed by caloric (hot, cold ± ice water) stimulation. Indeed, caloric stimulation has long been considered ‘a gold standard’ in the measure of vestibular function. Specifically caloric stimulation involves the instillation of air or water above or below body temperature into the external auditory canal and causes movement of fluid within the horizontal SCC. This movement of fluid leads to perceived rotation about the axis of the horizontal canal and the generation of compensatory horizontal nystagmus (Halmagyi, Curthoys et al. 2004) as a result of the VOR. With caloric stimulation, each ear can be tested individually and the responses can be compared. Typically horizontal canal function is judged based on: 1) the velocity and number of beats of nystagmus recorded and 2) the difference in the velocity of the nystagmus between the 2 ears. The limits of normal and abnormal responses will be further described in the Chapter 2: Methods.

The integrity of horizontal canal function can also be assessed by measuring the VOR in response to rotation. A rotational stimulus can be administered through several means, the most standardized being the use of a rotational chair. The use of sinusoidal harmonic rotation allows for the measurement of the horizontal VOR. Rotational testing however may miss a unilateral decrease or loss of horizontal canal function given that it is measuring a signal (i.e. VOR gain) that is subject to physiologic compensation. For example, a patient with a unilateral loss of
horizontal canal function may yield any of the following results 1) decreased VOR gain as the head is rotated toward the lesioned side, 2) bilateral decreased VOR gain or 3) bilaterally normal VOR gain, depending on the degree of dysfunction and subsequent compensation that has occurred. Just as the auditory system operates over a wide range of sound frequencies, the vestibular system also operates over a range of motion frequencies. For example the SCC’s are sensitive to a frequency range of angular accelerations between 0.10 Hz to 10 Hz with low frequency performance extended to 0.01 Hz through central mechanisms (Carey and Della Santina 2005; Newlands and Wall III 2006). One of the deficiencies of using a caloric stimulus to assess horizontal canal function is that it measures the lowest frequencies within the functional range of the horizontal canal (0.002 to 0.004 Hz) and as such does not reflect the ‘real world’ operating range of the system (0.5 to 7 Hz) (Hess, Baloh et al. 1985; Shephard and Telian 1996; Hamid 2000). The use of a high frequency rotational stimulus improves on caloric stimulation in that it allows access to responses to higher frequencies of motion, including those that fall within this ‘real world’ range. Measuring the responsiveness of the system to high frequency motion is important given that abnormalities in some symptomatic patients might only be revealed using high frequency rotational testing (Prepageran, Kisilevsky et al. 2005).

Although much of the adjunctive vestibular end organ testing focuses on the horizontal canal, assessment of saccular function and the sacculocollic pathway is possible through the use of the vestibular evoked myogenic potential (VEMP). The VEMP response is a transient, biphasic, short latency muscle relaxation potential generated by the synchronous discharges of motor units within the sternocleidomastoid (SCM) muscle in response to a loud sound, most often a click. This myogenic potential is felt to reflect a disynaptic vestibulocollic reflex originating in the saccule and transmitted via the ipsilateral medial vestibulospinal tract to sternocleidomastoid motoneurons (Kushiro, Zakir et al. 1999). It is presumed that the VEMP arises from the saccule given that this is the vestibular end organ that is most sensitive to auditory stimulation (Young, Fernandez et al. 1977; Didier and Cazals 1989) and click sensitive neurons in the vestibular nerve also respond to tilts and are generally located in the saccular macula (Murofushi, Curthoys et al. 1995; Murofushi and Curthoys 1997).

In addition to caloric, rotational and VEMP testing, there are a number of adjunctive vestibular tests have been described, that have not yet made their way into the mainstream.
These include tests of the otolith-ocular reflex measured using off-vertical axis rotation (Vibert, Hausler et al. 2001) and high frequency/acceleration linear head heave tests (Kessler, Tomlinson et al. 2007). In the present study we have chosen to assess horizontal canal function using both caloric and rotational testing in an effort to span nearly its entire frequency range, as well as saccular function using VEMP testing.

It is presently unclear which of the clinically available tests of vestibular function provides the best and most meaningful measures of end-organ function in children. In addition, investigating the relationship between auditory, vestibular, and balance dysfunction in children with congenital or early acquired sensorineural hearing loss (SNHL) carries with it the potential risk of confounding due to developmental changes in vestibular function that may occur early on. Minimizing this risk requires a thorough understanding of the time course to maturation of the vestibular end-organs and their measurable responses and this topic will be specifically addressed in the following section.

1.5 Anatomic and functional development of the inner ear

The structural components of the inner ear develop early on in gestation (Bergstrom 1973). The bony construct of the vestibule is complete by the 10th week and that of the cochlea by the 11th week of gestation. The membranous labyrinth is fully developed in the vestibule by approximately the 12th week and in the cochlea by approximately the 28th week of gestation. While anatomic maturity is reached early on in gestation there is also evidence that functional maturation occurs early in life (Bárány 1918; Thornval 1921; Eviatar, Eviatar et al. 1974; Ruben 1992). Auditory function, measured by the auditory brainstem response (ABR), has been recorded as early as the 26th week of gestation, however, maturation of those responses, as reflected by decreases in threshold and latency, occur over the course of the first year of life (Ruben 1992). Similarly, the vestibular system exhibits responsiveness, although not complete maturation, early on in the neonatal period. In the early twentieth century, Bárány stimulated newborns by rotation and observed movements of the head in the direction of the slow component of the nystagmus. He also demonstrated that visual fixation could overcome the vestibular response by three days of age (Bárány 1918). In 1921, Thornval et al. stimulated the horizontal canals of 74 newborns with 20°C water and observed nystagmus in all infants.
(Thornval 1921). The response of the vestibular system to external stimulation does however demonstrate some variation with age (Ornitz, Atwell et al. 1979), and some full term infants may lack a nystagmic response to either rotation or caloric stimulation. Overall, the intensity of nystagmus increases with age, while latency decreases with duration of gestation and age, suggesting a physiological maturation of the peripheral system over time. Nystagmus induced by ice water (the most extreme of the caloric stimuli used to illicit this response) reaches comparable levels in all children by 6 months of age except in premature infants who show comparable responses by approximately 9 months of age. In general, maturation of the vestibular responses parallels acquisition of head and postural control as well as appearance of righting responses correlating well with birth weight and length of gestation (Eviatar, Miranda et al. 1979). One of the largest series of vestibular testing in infants and children found that complete maturation of the labyrinthine system is reached around 18 to 24 months of age with little variation occurring thereafter (Eviatar, Eviatar et al. 1974). Relative to the developmental time course of the labyrinth, the visuo-vestibular pathways demonstrated a prolonged time-course to maturation with some ocular motor tasks (i.e. smooth pursuit) not reaching maturity until the teenage years (Herman, Maulucci et al. 1982). In addition to maturational changes that occur over time, differences in the characteristics of nystagmus generated by the neonate and young child compared to adult patterns, during tests of vestibular function also exist. Several studies confirm that the speed of the slow component is the best measure of peripheral vestibular function in the paediatric population. The rationale for this is that the correlation between duration of nystagmus and amplitude and speed of the slow component is poorer in this group, with younger infants tending to display shorter duration but higher amplitude nystagmus (Mitchell and Cambon 1969; Tibbling 1969). Likewise several neonatal studies have demonstrated that the fast phase of nystagmus cannot be reliably elicited by either rotation or caloric stimulation until 45 weeks gestational age (Mitchell and Cambon 1969; Eviatar, Eviatar et al. 1974; Donat, Donat et al. 1980; Rossi, Solero et al. 1998). A large study of caloric testing in children 5 to 14 years of age demonstrated similar ranges for directional preponderance and canal paresis by caloric testing in adult and pediatric patients ((Kenyon 1988)) and these results were in line with the definitions described by Jongkees (Jongkees 1973). Measurement of horizontal canal function by examining the VOR in response to rotation in several groups of normal children has yielded results that are very similar to those for adults, cautiously
suggesting a relatively early maturation of the VOR and the appropriateness of using adult normative data in defining responses particularly after 6 months of age (Eviatar, Miranda et al. 1979; Ornitz 1983; Peterka, Black et al. 1987; Horak, Shumway-Cook et al. 1988).

In summary, the vestibular system is responsive at birth, although some variations in function, as measured by the VOR, occur with age. Maturation of the VOR appears to occur early in post-natal life and certainly by 6 to 9 months of age infants produce responses that are, for the most part, quantitatively similar although qualitatively different than that of adults supporting the use of normative data obtained from adult populations in the current study.

While the current section supports the notion that it is reasonable to test vestibular function in infants and young children, the following section addresses the important consideration of whether we can do so reliably.

1.6 Reliability and limits of testing vestibular and balance function in children

“The testing of children rarely fulfills all the conditions for an ideal vestibular study” (Rapin 1974). This quote certainly reflects the sentiment that surrounds testing of any kind in a pediatric clinical setting. A number of modifications to adult neuro-otologic testing techniques have been suggested in the literature (Eviatar and Eviatar 1978; Snashall 1983; Cyr, Brookhouser et al. 1985). Yet, despite modifications in technique, caloric or rotational chair testing of young children often yields only qualitative results. Qualitatively normal results can be quite helpful while qualitatively abnormal results may only signal the need for repeat testing at an older age (Rapin 1974). In cases where quantifiable results are obtained, we must ask: How accurate are these results? Several studies have addressed this issue by examining the test-retest reliability of vestibular tests performed in children. In a study of caloric function in neonates, repeat caloric tests within 24 hours produced identical results (Donat, Donat et al. 1980). Similarly, in children over the age of 5, the test-retest reliability was found to be excellent (Kenyon 1988). These two studies however did not include children aged 12 to 36 months which represents the most challenging group for testing. When this group was included, the disagreement between caloric ENG testing was as high as 24%, where an initial absent response was followed by a positive response in all cases (Rapin 1974). Age and patient compliance were most certainly an issue in these false negative responses with two of the
children in the above study being 18 months of age. In addition to age, a multitude of other factors predispose children to false negative results on tests of vestibular function; malposition of irrigation tubing, presence of cerumen, crying, agitation and inadequate mental tasking, among others have been found to impact vestibular test results in children (Rapin 1974). In addition to these issues, inattention and frequent random eye movement are more common in children and create difficulties in the analysis of the ENG traces obtained during a caloric or rotational stimulus which often require a trace by trace analysis (Snashall 1983). Vestibular testing in hearing impaired children might be further complicated by the demonstrated ability of this group in particular to suppress nystagmic responses. In children with hearing loss, normal nystagmic responses present during a mental alerting task have been shown to be rapidly eliminated when tasking is stopped. Therefore, inadequate tasking carries with it the risk of inappropriately labeling a child with reduced or absent vestibular responses (Brookhouser, Cyr et al. 1982). Despite these challenges, clinicians have succeeded in performing the gamut of vestibular function tests in even the most challenging paediatric patients and the importance of repeated testing should be underscored and testing likely becomes more straightforward as the children age.

Assessment of horizontal canal function by sinusoidal, harmonic acceleration, rotational chair testing may be less affected by age. This is an accurate and non-aversive tool to assess vestibular function in infants and children as young as 2 days of age as all subjects older than 9 months have been shown to generate consistent nystagmic responses over a range of frequencies (Staller, Goin et al. 1986). This finding supports a short maturational time course of the VOR (as reviewed in Section 1.3). The gain, phase and symmetry in children (3 months to 6 years of age) are similar to the currently established adult normative values during harmonic sinusoidal rotation at 0.08Hz. No significant differences were detected in the gain, phase, and symmetry of the responses of full term versus premature infants (Cyr, Brookhouser et al. 1985).

Measurement of saccular responses using vestibular evoked myogenic potentials has been successful in young children 3 to 11 years of age. Normative data has also been established and high compliance with testing has been seen. Some difficulty with maintaining head elevation throughout the test does occur and, as will be described in the Results (section 3.1) and most children find the test difficult. The latencies of the VEMP amplitude peaks (the
p1 and nI waves) are significantly shorter with decreasing age, particularly for the negative peak (nI), and age needs to be considered when determining the appropriate time window to record and detect these responses (Kelsch, Schaefer et al. 2006).

Irrespective of the test used, the variability of response measures will be greater in children than in adults. Testing paradigms in children undoubtedly require numerous modifications with overall testing taking more time. Certainly the period between 12 to 36 months has been identified as an age group in whom vestibular testing is particularly challenging.

We have spent a significant amount of time outlining the anatomy and physiology of the vestibular end organs and how we measure their function while addressing the unique aspects of testing function in the paediatric setting. We will now shift focus and begin looking more closely at what is already known about the relationship between auditory, peripheral vestibular and balance function in children.

1.7 Relationship between sensorineural hearing loss and vestibular function

The importance of studying the relationship between peripheral vestibular function in the setting of deafness is underlined by the fact that sensorineural hearing loss is the most common congenital sensory impairment occurring in 3 out of every 1000 live births (NCHAM 2006). Should even a small proportion of these individuals with SNHL exhibit concurrent vestibular involvement, this would still account for large numbers of individuals with vestibular dysfunction requiring identification, education and therapy.

A number of studies have examined vestibular function in large cohorts of children with hearing impairment and we will summarize their findings in the following section. Although these studies provide a good foundation of knowledge for the current investigation, their success in accurately defining the relationship which exists between SNHL and vestibular function in children is hindered by the significant heterogeneity within their cohorts. More specifically, considerable variability with respect to degree and etiology of the hearing loss, as well as in the measurement and quantification of the vestibular responsiveness. In an effort to add to the current body of knowledge, in the current study we will aim to control these variables in an attempt to parse out the relationship between auditory, vestibular and balance function.
1.7.1 Incidence of vestibular lesions amongst those with cochlear lesions

Documentation of vestibular function and dysfunction in children with hearing impairment has a long and rich history which has indicated that somewhere in the range of 20 to 85% of children with hearing loss demonstrate some form of vestibular end organ dysfunction (Guilder and Hopkins 1936; Arnvig 1955; Goldstein, Landau et al. 1958; Everberg 1960; Rosenblut, Goldstein et al. 1960; Sandberg and Terkildsen 1965; Rapin 1974; Holderbaum, Ritz et al. 1979; Kaplan, Goddard et al. 1981; Brookhouser, Cyr et al. 1982; Potter and Silverman 1984; Horak, Shumway-Cook et al. 1988; Black, Shupert et al. 1989; Huygen, van Rijn et al. 1993; Gasparini, Estivill et al. 1999). This extensive range is likely a reflection of the variety of methods used to quantify vestibular dysfunction and the characteristics of the study populations, particularly with respect to the degree and etiology of the hearing impairment. The main conclusions that can be drawn from much of the current literature were insightfully summarized by Guilder and Hopkins in their 1935 study examining vestibular responses in children attending a school for the deaf. They noted that with the exception of meningitis, it was absolutely impossible to forecast the vestibular response of a child based on their etiology of deafness. They saw a range of vestibular responsiveness that spanned from absent to normal across their designated etiologic subgroups, as well as across different categories of residual hearing (Guilder and Hopkins 1936).

Just as the degree of hearing loss can span the spectrum of mild to profound, unilateral to bilateral, vestibular function similarly has a wide spectrum of findings. Some cohorts demonstrated a mix of partial versus complete vestibular dysfunction (Rosenblut, Goldstein et al. 1960), while others suggested that a partial vestibular lesion in the presence of total deafness is rare (Everberg 1960). Numerous studies have also shown that vestibular dysfunction can be unilateral versus bilateral and does not always correlate with the sidedness of the auditory loss (Everberg 1960; Rosenblut, Goldstein et al. 1960; Brookhouser, Cyr et al. 1982; Huygen, van Rijn et al. 1993).

1.7.2 Etiologic differences and the combined audiovestibular loss

The vestibular phenotype of a number of congenital, hereditary and acquired causes of SNHL have been defined. These include, among others, Usher’s Syndrome type I, which is
associated with bilateral vestibular loss, as well as bacterial meningitis where the SNHL is often accompanied by profound vestibular dysfunction (Kaplan, Goddard et al. 1981; Kumar, Fishman et al. 1984; Karjalainen, Terasvirta et al. 1985; Samuelson and Zahn 1990; Otterstedde, Spandau et al. 2001). Well-defined syndromes and acquired infectious losses, however, account for only a small percentage of all SNHL, with the etiology of deafness being either unknown or due to a non-syndromic genetic cause in the majority of children (Propst, Papsin et al. 2006). Despite very little literature on the topic, there is a general feeling that non-syndromic recessive causes of deafness, of which the most common are defects in the GJB2 gene, are not typically associated with concurrent deficits in vestibular end organ function (Todt, Hennies et al. 2005).

The variability in vestibular responsiveness across different etiologies of SNHL is readily apparent in the available literature. This incredible variability is present even within a single etiologic category such as deafness secondary to meningitis even though the relationship between auditory and vestibular function in this setting is thought to be better understood. Children with SNHL due to meningitis demonstrate a disproportionately large degree of vestibular non-responsiveness; however the degree of non-responsiveness does range from unilateral weakness to bilateral areflexia of the horizontal canals (Huygen, van Rijn et al. 1993). Similarly, cases have been documented where nearly half of the children with profound SNHL due to meningitis demonstrated normal horizontal canal function as measured by a caloric stimulation (Rapin 1974).

One might expect the relationship between vestibular and auditory dysfunction to be relatively straightforward in the setting of inner ear dysplasia. In many cases vestibular dysfunction correlates well with the presence of inner ear dysplasia on CT imaging, however overall, equal numbers of children with normal vestibular function were found in both the radiologically normal group as in the radiologically abnormal group (Diepeveen and Jensen 1968).

Not all children with hearing loss due to inner ear dysplasia or acquired infectious causes such as meningitis demonstrate complete vestibular areflexia (Diepeveen and Jensen 1968; Rapin 1974). Similarly, some children whose SNHL is not due to meningitis, have bilateral vestibular dysfunction (Huygen, van Rijn et al. 1993). In the literature, reports of
complete bilateral loss of vestibular function have been associated with SNHL due to thalidomide fetopathy, Kernicterus, cytomegalovirus, as well as non-syndromic autosomal recessive type hearing loss and hearing loss of unknown etiology (Huygen, van Rijn et al. 1993). The prevalence of vestibular disorders amongst these other etiologies is highlighted in studies which excluded children whose deafness was secondary to meningitis or other severe infantile infection (Rosenblut, Goldstein et al. 1960). Despite this exclusion, Rosenblut and colleagues reported that a large proportion (43%) of the remaining cohort demonstrated vestibular dysfunction (Rosenblut, Goldstein et al. 1960).

Just as SNHL can occur in both the presence and absence of concurrent vestibular defects, vestibular deficits can appear in individuals with and without SNHL. Verhagen et al., for instance, report on familial congenital vestibular areflexia occurring in the absence of hearing loss (Verhagen, Huygen et al. 1987).

Variability in the relationship between auditory and vestibular function can certainly be linked to differences in the etiology of the inner ear disorder. In addition to etiology however, the degree of SNHL may also aid in predicting the likelihood of an associated loss of vestibular function.

### 1.7.3 Relationship between hearing thresholds and vestibular function

Although the relationship between vestibular and auditory function is not simple, they do appear to be associated. A number of studies have shown that, at least on a group level, the likelihood of a vestibular impairment relates to the degree of the hearing loss (Goldstein, Landau et al. 1958; Rosenblut, Goldstein et al. 1960; Sandberg and Terkildsen 1965; Brookhouser, Cyr et al. 1982; Huygen, van Rijn et al. 1993). As a group, children with normal vestibular function, as measured by caloric stimulation, have lower pure-tone averages (PTA) than both those with unilateral vestibular hypofunction who in turn have higher PTA’s than those with bilateral vestibular hypofunction (Brookhouser, Cyr et al. 1982). Likewise the proportion of individuals with vestibular impairment is significantly lower (20 to 36%) in children with hearing threshold of less than 90dB and higher (80%) in those with more severe hearing loss (Sandberg and Terkildsen 1965; Huygen, van Rijn et al. 1993). Although the literature supports the significant relationship known to exist between concurrent depression of
hearing sensitivity and vestibular responsiveness, hearing thresholds are not predictive for the individual case. More specifically, Rosenblut et al. demonstrate in their cohort that 16.1% of children with relatively good auditory sensitivity demonstrated complete absence of vestibular function, while 43.3% of the children with the poorest auditory sensitivity had normal responses (Rosenblut, Goldstein et al. 1960).

The relationship between auditory and vestibular function is certainly complex. The intricacy of this interaction is particularly evident in cases where vestibular function is well preserved in the presence of even the most severe auditory dysfunction and in instances where apparently minor losses of auditory function are accompanied by complete vestibular dysfunction.

1.7.4 Relationship between tests of vestibular end organ function and balance in the setting of SNHL

Clinically, the importance of vestibular function testing is to provide an indication of the child’s ability to achieve and maintain adequate static and dynamic balance to participate in daily activities. However, the functional correlates of vestibular end organ dysfunction are much less commonly measured and reported in the literature. The maintenance of posture and the control of gait are complex functions that rely on the appropriate acquisition of motor control patterns with feedback modulation resulting from inputs to and from the vestibular, visual, and somatosensory systems. The labyrinths are known to play a role in postural responses (Mergner and Rosemeier 1998) and therefore it is natural to think that their hypofunction would lead to delays in the acquisition of gross motor milestones. While the failure to acquire language alerts us to hearing disorders, failure to achieve motor milestones should alert us to potential vestibular dysfunction. The motor clues that lead us to suspect vestibular dysfunction may be subtle and include delay of gross motor development such as sitting and walking, head tilt, ‘floppy’ or weak neck, ‘wobbly’ head and crawling with head hanging. These children may be labeled as uncoordinated, awkward or clumsy. While even children with the most profound losses routinely achieve adequate gait, they may fail in older age to develop the skills necessary for higher order motor functions such as skating or riding a bicycle. Although some studies have examined motor function in deaf children, the etiology
and degree of the SNHL are often variable and there can be a wide range of severity and type of vestibular dysfunction. As a result the relationship between specific deficits of the peripheral vestibular system and deficiencies in motor-co-ordination have been difficult to establish. As a group, children with profound SNHL do tend to perform more poorly on tests of gross motor or balance activities compared to their normal hearing peers (Rapin 1974; Potter and Silverman 1984; Cushing SL 2007). There are several ways to assess static and dynamic balance as well as motor development in children. This assessment can be as simple as recording motor milestones or as complicated as computerized dynamic posturography (CDP) although the goal is the same. It has been demonstrated that motor milestones such as sitting, cruising and walking are often, although not always, delayed in children with vestibular hypo/non-function (Rapin 1974). In a group of children with SNHL of varying etiology and decreased or absent responses on caloric testing, the age at which children first began to sit, where documented, ranged from 6 to 24 months (µ=10.6 months) and first steps occurred at age ranges of 10 to 48 months (µ=20 months), with nearly half of the group walking at 18 months or later (Rapin 1974). However, in the same study, some children with absent responses bilaterally and confirmed by repeated testing walked at a normal age. Therefore caution must be taken in assuming that the emergence of walking at a normal age negates the presence of a significant vestibular disturbance (Rapin 1974). At older ages, these children may appear normal on neurological examination; however, challenging activities such as walking in tandem or standing on one foot often remain quite difficult.

Even children with the most extreme dysfunction of the peripheral vestibular end organs, such as the absence of one or more semicircular canals, eventually reach their motor milestones, although later than anticipated. Despite an absence of response to caloric stimulation, some children without horizontal canals have been shown to demonstrate nystagmus, although weakly, following rotation with the assumption that these responses may be attributable to function of the remaining vestibular end organs. Interestingly, those children who demonstrated weak but present nystagmus to rotation achieved independent walking at an earlier age than those who did not. Therefore, motor function and development in children with inner ear anomalies may be better correlated with the response to a rotational stimulus than a caloric stimulus (Tsuzuku and Kaga 1992).
Beyond recording motor milestones, a number of clinical manoeuvres exist to assess static balance, one of which includes the Romberg test. The Romberg test measures the ability to maintain standing balance and requires the subjects to stand upright, feet together, arms outstretched palms facing upward with their eyes open and then closed. A comparison between responses to caloric stimulation and performance in a standard and modified Romberg demonstrated that the standard Romberg, even with eyes closed, was of little benefit in the identification of bilateral or unilateral caloric weaknesses. However, performance during a tandem Romberg using the Jendrassik manoeuvre (hands are hooked together by flexed fingers while attempting to pull them apart) which increased the difficulty of the test, was more consistent with caloric test abnormalities in a significant number of subjects (Brookhouzer, Cyr et al. 1982). Using an equivalent to the standard Romberg test, Horak et al found that they could not differentiate the control group from the hearing impaired group despite the presence of reduced peripheral vestibular function in the hearing impaired patients (Horak, Shumway-Cook et al. 1988). Additional tests used commonly to assess static balance include rail walking and one-foot standing with eyes open and eyes closed (Myklebust 1964; Scanlon and Goetzinger 1969; Lindsey and O'Neal 1976; McCarron and Ludlow 1981; Potter and Silverman 1984). No clear relationship has been established between reaction to caloric stimuli and the rail walking test (Davey 1954). Similarly, despite a high prevalence of hypoactive/absent vestibular responses, and poor performance on tasks of standing balance in a profoundly deafened cohort, no significant association between the rotationally induced horizontal canal response and standing balance performance has been found. On this task, as a group, deaf children with no observable vestibular response performed no worse than children with normal or hypoactive vestibular function in regard to standing balance with or without vision (Potter and Silverman 1984).

Computerized dynamic posturography (CDP) is a technique that allows for the assessment of postural stability while allowing for controlled alterations of the sensory environment. During this test, subjects stand on a computer-controlled platform within a visual surround. The platform contains force plates which measure sway, changes in the centre of gravity and the distribution of force across the feet. Both the platform and the visual surround can be moved and a foam spacer can be placed between the subject’s feet and the platform to
alter proprioception. The ability to remove and alter sensory inputs such as vision and proprioception allows for the assessment of the relative contributions of different sensory information to the maintenance of balance in a given patient. Unfortunately, even children with normal vestibular function under the age of 5 to 7 years, typically fall in conditions when vision and surface inputs are eliminated and/or inaccurate. Therefore, to date, posturography has limited sensitivity in younger children (Shumway-Cook and Woollacott 1985). Correlations

<table>
<thead>
<tr>
<th>Balance Subtest Items</th>
<th>Maximum Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing with feet apart on a line</td>
<td></td>
</tr>
<tr>
<td>Eyes Open</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Eyes Closed</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Walking forward on a line</td>
<td>6 steps</td>
</tr>
<tr>
<td>Standing on one leg on a line</td>
<td></td>
</tr>
<tr>
<td>Eyes Open</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Eyes Closed</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Walking forward heel to toe on a line</td>
<td>6 steps</td>
</tr>
<tr>
<td>Standing on one leg on a balance beam</td>
<td></td>
</tr>
<tr>
<td>Eyes Open</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Eyes Closed</td>
<td>10 sec.</td>
</tr>
<tr>
<td>Standing heel-to-toe on a balance beam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 sec.</td>
</tr>
</tbody>
</table>

Table 1.1. Bruininks-Oseretsky Test of Motor Proficiency 2 (BOT-2) Balance Subtest Items and grading scheme.

between peripheral vestibular function, postural stability measured using CDP and motor proficiency have been examined in a group of children with varying degrees of SNHL of different etiologies (Horak, Shumway-Cook et al. 1988). In this study, vestibular function was assessed by measuring the VOR which was stimulated by rotation at two frequencies (0.2 and 0.05Hz). Motor proficiency was evaluated by means of selected subtests of the standardized Bruininsk-Oseretsky Test of motor proficiency (BOT) (Bruininks and Bruininks 2005). The BOT is one of the most commonly used, age standardized test of motor function. It contains a number of subtests designed to assess gross motor and fine motor skills in children over 4 years of age. A number of the subtests are relevant to the study of peripheral vestibular function, in particular the balance subset which contains 9 balance related tasks performed with eyes open and closed (Table 1.1).

In Horak et al.’s study, the entire BOT test battery was administered which includes tests of running speed and agility, fine motor coordination among others. The beauty of this test is
that it has been standardized and population norms by age are provided. In the current study, children with SNHL and peripheral vestibular dysfunction defined by an abnormal VOR, demonstrated significant instability on posturography but only in conditions where they were forced to rely on vestibular inputs for orientation (i.e. where normal visual and proprioceptive cues were disrupted). With the exception of balance scores, where children with audiovestibular losses scored half that of the normal group, motor proficiency was otherwise normal. Although not statistically tested, there appeared to be a relationship between the severity of the vestibular loss and balance ability reflected in the BOT balance subset score, with the lowest balance scores belonging to children with bilateral absent peripheral vestibular function. Interestingly children with complete bilateral vestibular dysfunction had higher scores in running speed, bilateral coordination and strength than many of the children with reduced but not absent vestibular function. Several children with hearing impairment, however, demonstrated a very different type of balance impairment. Despite demonstrating a normal peripheral vestibular function based on an appropriate VOR on rotational testing, they presented with presumed abnormalities in central sensory organization in that they were unstable under all conditions using CDP and all aspects of motor proficiency as measured by the BOT were abnormal. In summary, in children with SNHL, reduced or absent vestibular function did not prevent the development of normal motor performance except in specific vestibular dependent balance activities. In addition, reduced sensory function in the peripheral vestibular apparatus had a very different effect on balance and co-ordination than presumed deficits in sensory organization which led to much more significant functional consequences (Horak, Shumway-Cook et al. 1988).

The reviewed literature suggests that motor skills develop, although at times on a protracted timeline, even in the complete absence of peripheral vestibular function. As a result, clinically significant vestibular dysfunction is easily overlooked in children with congenital or early onset severe to profound hearing impairment. This is especially true given that hearing and vestibular impairments are not reflected in scores on tests of fine motor co-ordination and visual motor coordination (Geddes 1978; Holderbaum, Ritz et al. 1979; Brunt and Broadhead 1982) but rather surface only on tasks that discretely isolate reliance on sensory vestibular input (Horak, Shumway-Cook et al. 1988). The balance subset of the BOT (Table 1.1) appears to be
particularly well suited to identify vestibular dysfunction in children with SNHL in comparison to a number of other clinical tests (Crowe and Horak 1988). In particular, those items that involve standing across a narrow balance beam limiting ankle torque and disabling the ability of children with peripheral vestibular dysfunction to adjust their body center of mass using hip movements, provide the difficulty level required to uncover vestibular deficits in this group (Supance and Bluestone 1983). However a clear and consistent relationship does not appear to exist between vestibular function as measured by the limited tests of vestibular end organ function and functional balance related performance.

The current and previous sections have provided an overview of what is currently known about the relationship between auditory, vestibular and balance function in children with SNHL. With respect to the current study, in an effort to control for the severity of the auditory deficit, we have chosen to study this relationship in children with unilateral cochlear implants, all of whom exhibit severe to profound bilateral SNHL by candidacy criteria for implantation. Although this provides adequate control for degree of SNHL, it brings with it the possibility that peripheral vestibular function and balance may be affected by either implantation or the use of a cochlear implant. The likelihood, nature and magnitude of such potential effects of implantation on vestibular function will therefore be addressed in the subsequent section.

1.8 Implantation and vestibular function

A cochlear prosthesis is an implanted electronic device that is designed to provide direct electrical stimulation to the primary auditory afferents that lie within the osseous spiral laminae, providing an auditory percept in the setting of severe to profound SNHL. The relative placement of all components of the cochlear implant are depicted in Figure 1.6. Specifically at the time of surgery the scala tympani is entered at the base of the cochlea, with exposure of the inner lining of the scala tympani and the electrode array is inserted. The cochlear implant itself consists of 22 platinum electrode bands placed 0.45 mm apart and located on a silastic matrix. Depending on the nature of the auditory signal detected by an ear level microphone and coded by the implant processor, a combination of these electrodes are activated, causing stimulation of the primary auditory afferents and ultimately leading to an auditory percept. Just as anomalies of the auditory system due to genetic defects, meningitis or other causes may be associated with
parallel injuries of the vestibular end organs, so too might cochlear implantation iatrogenically cause injury to the vestibular system. More recently, evaluation of vestibular end organ function in the setting of profound SNHL has garnered increased attention because of its relevance to the topic of bilateral cochlear implantation and the potential risk of bilateral vestibular injury that this intervention carries. There are a number of mechanism by which the act of cochlear implantation or any inner ear surgery for that matter may disturb vestibular function. The vestibular dysfunction that ensues following inner ear procedures which are not aimed at

**Figure 1.6.** Relative placement of cochlear implant components. Inset demonstrates placement of cochlear implant electrode array within scala tympani. (From (Papsin and Gordon 2007))

vestibular ablation (i.e. cochlear implantation, stapedectomy etc.), are felt to lead to either a partial to complete deafferentation of the vestibular end-organs (Spector 1973; Molony and
Specifically, these surgically induced injuries to the labyrinthine may occur secondary to 1) the induction of a serous labyrinthitis due to opening of the membranous labyrinth 2) the introduction of blood into the inner ear 3) mechanical injury due to the insertion of the electrode array 4) high speed drilling within the temporal bone, amongst others. Although the electrode array itself and its insertion appears quite delicate, in reality cochlear implantation has been shown to lead to mechanical disruption of inner ear structures including, rupture of the basilar membrane, fracture of the osseous spiral lamina, transection of the scala media and fracture of the modiolus (Kennedy 1987; Welling, Hinojosa et al. 1993; Gstoettner, Plenk et al. 1997; Rossi and Bisetti 1998; Richter, Aschendorff et al. 2001; Richter, Jaekel et al. 2001; Eshraghi, Yang et al. 2003). More specifically with respect to the histopathology of the vestibular end-organs following implantation, fibrosis, hydrops with saccular membrane distortion, osteoneogenesis and reactive neuromas were noted in the vestibule and semicircular canals (Tien and Linthicum 2002). However, these histologic injuries did not translate into physiologic dysfunction in all cases (Tien and Linthicum 2002).

In addition to structural injuries of the labyrinth following cochlear implantation, measurable damage to vestibular function following cochlear implantation has also been described (Black 1977). However, permanent loss of vestibular function post-implantation is relatively uncommon despite the obvious risk of labyrinthine damage that accompanies the insertion of the implant’s electrode array into the cochlea (Chiong, Nedzelski et al. 1994; Brey, Facer et al. 1995; Ribari, Kustel et al. 1999; Kubo, Yamamoto et al. 2001; Szirmai, Ribari et al. 2001; Vibert, Hausler et al. 2001; Fina, Skinner et al. 2003; Buchman, Joy et al. 2004; Migliaccio, Della Santina et al. 2005). Although there are numerous reports of pre and postoperative vestibular function in profoundly deaf adults receiving cochlear implants, there is a paucity of data regarding vestibular function in children with profound SNHL receiving cochlear implants. Given the relationship between auditory and vestibular dysfunction that we have been discussing up until now, the effect of cochlear implantation on vestibular function needs to take into account the incidence of pre-operative vestibular dysfunction in cochlear implant candidates. The reported rates of horizontal canal dysfunction as measured by caloric stimulation varies widely from 25 to 100% (Black 1977; Eisenberg, Nelson et al. 1982; Chouard, Fugain et al. 1984; Black, Lilly et al. 1987; Magnusson, Enbom et al. 1991; van den
Broek, Huygen et al. 1993; Chiong, Nedzelski et al. 1994; Huygen, van den Broek et al. 1994; Brey, Facer et al. 1995; Himi, Shintani et al. 1997; Ito 1998; Rossi, Solero et al. 1998; Ribari, Kustel et al. 1999; Hoffman 2000; Kiyomizu, Tono et al. 2000; Schneider, Schneider et al. 2000; Kubo, Yamamoto et al. 2001; Szirmai, Ribari et al. 2001; Vibert, Hausler et al. 2001; Higgins, Chen et al. 2002; Fina, Skinner et al. 2003; Buchman, Joy et al. 2004; Enticott, Tari et al. 2006; Bodmer, Shipp et al. 2007) with this range narrowing slightly from 23% to 76% when only studies with larger numbers (n > 15) are included (Huygen, Hinderink et al. 1995; Kiyomizu, Tono et al. 2000; Vibert, Hausler et al. 2001; Fina, Skinner et al. 2003; Buchman, Joy et al. 2004; Enticott, Tari et al. 2006). The largest series measuring vestibular function in children to date was published by Buchman et al. in 2004 and included a total of 22 children. In this pediatric cohort, 68% demonstrated vestibular dysfunction as indicated by absent or low intensity responses from the horizontal canal to caloric irrigation pre-operatively (Buchman, Joy et al. 2004). Using low frequency rotational chair testing estimates the incidence of unilateral vestibular deficits to be approximately 14% and bilateral deficits to be 28% in CI candidates (Chiong, Nedzelski et al. 1994; Vibert, Hausler et al. 2001). Those studies using velocity step tests report an incidence of approximately 3% of unilateral and 63% bilateral vestibular dysfunction in this population (Huygen, Hinderink et al. 1995).

Subjective complaints of dizziness following cochlear implantation occur in 2 to 49% of patients and are more likely to occur with increasing age in adulthood (Black, Lilly et al. 1987; Cohen, Hoffman et al. 1988; Webb, Lehnhardt et al. 1991; Huygen, van den Broek et al. 1994; Ito 1998; Kempf, Johann et al. 1999; Ribari, Kustel et al. 1999; Kubo, Yamamoto et al. 2001; Enticott, Tari et al. 2006). From a more objective perspective, the reported and estimated risk of losing or significantly diminishing horizontal canal function based on caloric testing post implantation ranges between 0 and 77% (Eisenberg, Nelson et al. 1982; Chouard, Fugain et al. 1984; Black, Lilly et al. 1987; van den Broek, Huygen et al. 1993; Chiong, Nedzelski et al. 1994; Brey, Facer et al. 1995; Huygen, Hinderink et al. 1995; Ito 1998; Rossi, Solero et al. 1998; Ribari, Kustel et al. 1999; Kiyomizu, Tono et al. 2000; Vibert, Hausler et al. 2001; Higgins, Chen et al. 2002; Buchman, Joy et al. 2004). However, these results vary with increasing duration between implantation and post-operative testing; this interval is important to consider as some individuals may exhibit a transient loss or decrease in function followed by
recovery (Vibert, Hausler et al. 2001). Longitudinal measures of horizontal canal function by caloric stimulus post-cochlear implantation suggest that by 4 months post-implantation caloric function has stabilized and few improvements in function occur subsequent to that (Buchman, Joy et al. 2004). In both adults and children, post implant vestibular function was reduced in 29% of those ‘at risk’ (i.e. those with normal or reduced but not absent horizontal canal function pre-implant in response to a caloric stimulus) of vestibular effects after CI. In this setting, significant reduction of vestibular function was defined as a reduction of the total caloric response of 21°/sec or greater. Changes in horizontal canal function as measured by a loss of caloric function were often paralleled by changes in VOR phase and gain in response to rotation (Buchman, Joy et al. 2004). Given the high degree of non- and hypo-functioning vestibular systems prior to implantation, Buchman suggests that the risk of a significant vestibular lesion secondary to implantation is quite low. In addition, he underlines the presumption that, in general, children have a greater capability to adapt to any injury to the vestibular system thereby decreasing the likelihood of a longstanding uncompensated vestibular defect as a result of bilateral cochlear implantation.

Similarly a significant reduction in horizontal canal function as measured by changes in VOR gain and phase to rotation, was seen in 14% of adults following unilateral cochlear implantation (Brey, Facer et al. 1995). In one of the most thorough evaluations of the horizontal and vertical semicircular canal function using head impulse testing, Migliaccio et al. demonstrated preoperative hypofunction of the horizontal canal in 36% and decreased gain in one or more of the vertical canals in 50%. Postoperatively, only a single patient (9%) experienced a significant decrease in function of all three semicircular canals on the implanted side accompanied by transient vertigo and oscillopsia (Migliaccio, Della Santina et al. 2005). Given that most studies to date have focused on the effect implantation on horizontal canal function, little is known about the impact of cochlear implantation on the otolithic organs. Fifty percent of children demonstrated bilaterally normal saccular function as measured by VEMP prior to surgery. Subsequent to implantation however, saccular function was felt to have been obliterated given the disappearance of VEMP responses in all children with the exception of one child who demonstrated a VEMP that was however smaller in amplitude than that seen pre-operatively (Jin, Nakamura et al. 2006). In comparison, utricular function measured using off-
vertical axis rotation, was not found to be impaired following cochlear implantation (Vibert, Hausler et al. 2001). Although age (>70 years) and a partial loss may increase the risk of a post-operative decrease in vestibular function, no consistent and reliable means have yet been established for determining the likelihood of experiencing a vestibular disturbance after implant surgery (Enticott, Tari et al. 2006).

Limited evaluation of the impact of implantation on static and dynamic balance has been performed to date however, some studies document a decrement in performance on the posturography test subsequent to implantation in roughly 11% (Brey, Facer et al. 1995) while others note small improvements in some individuals following implantation (Eisenberg, Nelson et al. 1982; Buchman, Joy et al. 2004). We have also demonstrated that children with SNHL and unilateral implants perform slightly, although significantly, better on the BOT-2 balance subset with their implants on versus their implants off although this certainly requires additional study with proper control of the directional information contained in the auditory signals presented to the implant (Cushing SL 2007).

1.9 Summary

The literature certainly suggests that a relationship exists between auditory and vestibular (dys)function in the setting of severe to profound SNHL. However, this relationship is not simple and is likely modulated by a number of factors including degree and etiology of SNHL. Keeping these factors in mind we will now set out the methods that we have chosen in our attempt to answer the following research questions:

1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?
2. What influence does etiology and time course of an inner ear injury have on this relationship?
3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?
4. Does cochlear implantation alter vestibular end organ function?
CHAPTER 2: METHODS

In the following sections I discuss the subject selection and various tests procedures used for our study followed by sections on data quantification and analysis. This project was approved by The Hospital for Sick Children Ethics Review Board and adheres to the “Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans”. Written consent and verbal assent were obtained from the guardians and children respectively.

2.1 Subjects

Forty children with profound SNHL sensorineural using unilateral cochlear implants (CI) participated in the study. The 22 boys and 18 girls ranged in age from 3 to 19.3 years (μ= 9.6 ± 4.6(SD)), all subjects were experienced users with at least one year of implant use (μ= 5.4 ± 2.6(SD)). Age at implantation was variable with a mean of 4.2 years (±3.6 (SD)). All children were using unilateral Nucleus 22, 24M, 24RCS, 24CA, and 24RE devices (Cochlear Corporation). Surgical insertion of the cochlear implant(s) were performed by two staff otolaryngologists at the Hospital for Sick Children. Table 2.1 details the etiology and time course of deafness in the children studied. While etiology was variable, most of the children (35/40) had a stable hearing loss while 4 experienced delayed onset of deafness due to progression of hearing loss from less severe to profound degrees. All children were otherwise developmentally normal and any child with a co-existing uncompensated visual loss or motor deficit was excluded from the study.

<table>
<thead>
<tr>
<th>Etiology of Deafness</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>7 (18)</td>
</tr>
<tr>
<td>GJB2</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Abnormal Cochlea</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Mondini Charge</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nature of SNHL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Progressive</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Progressive</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 2.1. Etiology and onset of SNHL in study population.
2.2 Assessment of horizontal semicircular canal function

2.2.1 Caloric stimulus

Horizontal semicircular canal function was first evaluated by caloric testing with electronystagmography (ENG) which was carried out by the Fitzgerald-Hallpike method of binaural alternating caloric stimulation following oculomotor and positional ENG (Fitzgerald and Hallpike 1942). Asymmetry of horizontal canal function was calculated based on peak slow-phase velocities using Jongkee’s formula (Jongkees 1973). All ears were inspected and debrided of wax prior to caloric testing. Abnormal horizontal canal function assessed by ENG-caloric testing was defined as follows:

1. Unilateral:
   a. Normal: < 15% excitability difference (ED)
   b. Mild loss: 15%-29% ED
   c. Moderate loss: 30%-50% ED
   d. Severe loss: 51%-100% ED

2. Bilateral:
   a. Normal: bithermal caloric responses >20º/sec
   b. Moderate: sum of bithermal caloric responses <20º/sec AND responses >3º/sec with ice water
   c. Severe: negative ice water caloric response on both sides

In order to facilitate adequate alerting throughout the test, one cochlear implant was left on and functioning during caloric testing. The ear-level microphone and processor were held away from the pinna and protected against water. The subjects were examined for the presence of spontaneous nystagmus in the dark, and gaze was tested in the usual gaze positions (left and right lateral, upward and downward gaze). Optokinetic nystagmus was assessed by moving a pattern of shadows projected on a hemicylindrical screen at a speed of 40 or 60º/s in a clockwise direction. An example of the ENG eye movement recordings obtained in the study is shown in Figure 2.1.
Figure 2.1  Eye position tracings obtained during ENG Caloric testing. (A) Smooth pursuit. (B) Active head shake. (C) Gaze testing (right). (D) Saccadic calibration in caloric test position (CTP). (E) Right beating nystagmus with an ice water stimulus ($10^\circ$) in left ear. (F) Left beating nystagmus with cold water stimulus ($30^\circ$) in right ear.
2.2.2 Rotational chair testing

Horizontal semicircular canal function was also assessed by evaluating the vestibuloocular reflex (VOR) gain in response to a rotational stimulus. The rotational stimulus was applied using a hydraulic rotational chair that was custom-built by Zonic Technical Laboratories Inc. in Cincinnati, Ohio. A hydraulic pump drives the chair with a 10-hp motor and a torque capability of 138 meters per kilogram. Each subject was seated alone with his or her head secured in padded clamps to couple head and chair movement tightly with the body, trunk, legs, ankles and shoulders were secured with chair belts. A booster pad was used for smaller children. Implants and hearing aids were removed during testing. Horizontal and vertical electro-oculography electrodes were placed at the lateral canthus, cheek and midbrow, with a ground electrode on the forehead. Calibration was performed using 10° gaze deviations to the right and left. All signals were amplified (band pass 0 to 30 Hz) and digitized. In most cases (29/36), sinusoidal harmonic acceleration testing was completed at a maximum rate of 100°/s with a frequency range of 0.25 to 5 Hz. In 4 children, pseudorandom rotation (0.32 to 5.01 Hz) was used. Both techniques were used with 3 children. At least two trials were attempted, the first in light and the second in dark. Additional trials were completed when results were equivocal or in the setting of poor compliance. In the VOR light (VVOR) paradigm, subjects were asked to fixate on a visual target on a tangent screen placed at 3.1 m. The VOR dark (VORD) was performed in total darkness with the patient instructed to fixate on a distant imaginary earth fixed target. Low frequency rotation was defined as frequencies ≤ 2 Hz whereas high frequency rotation was defined as frequencies > 2 Hz. The calibrated eye and chair cervo-feedback position signals were digitized online. During data analysis, eye position records were first edited to remove saccades. This was followed by differentiation of chair and cumulative eye positions to yield velocity profiles which then underwent power spectral analysis. The results were classified as abnormal when they were outside the normative data in at least two consecutive rotation frequencies. Normative data were obtained from healthy adult volunteers in our center and are previously reported (n=30, 8:22 men:women, mean age 27.2 years (Range : 20 to 45 years) (Mai, Dayal et al. 1986). All volunteers had normal corrected vision and had abstained from alcohol and other medications for 48 hours prior to testing. Abnormally low and high scores were defined as being beyond the 95% confidence interval.
2.3 Assessment of saccular function

Saccular function was assessed using the vestibular evoked myogenic potential (VEMP), a muscle reflex mediated through the vestibulocollic pathway (Figure 1.5). The VEMP was evoked using a 105 dB click, administered through Telephonics TDH-39 headphones (Telephonics Huntington, NY). All recordings were made on a Bio-logic Navigator SE system (Bio-logic Systems Corp., Illinois). Electrodes were placed at the mid-point of the muscle belly of the sternocleidomastoid (SCM) bilaterally with a reference electrode on the ipsilateral mastoid tip. Subjects were instructed to turn their head towards the contralateral side to activate the SCM. At least 100 sweeps within the acceptance criteria were averaged. Averaged signals were then replicated at least once. If head turning did not yield a tracing, the subjects were placed in a head lift position, activating both SCMs to increase the yield of testing (Kelsch, Schaefer et al. 2006; Wang and Young 2006). A VEMP response was judged as either present or absent. A range of acceptable latencies of the P1 N1 waveform were used (P1: 8.5 – 14 ms; N1: 15 – 23 ms) based on published age-appropriate ranges (Kelsch, Schaefer et al. 2006). An example tracing is shown in Figure 2.2.

![Figure 2.2](image_url)  
**Figure 2.2** Vestibular evoked myogenic potential obtained using parameters outlined above. Note the latency of the P1 (13 ms) and N1 (23 ms).
2.4 Static and dynamic balance testing

Dynamic and static balance was assessed using the balance subset of the Bruininks-Oseretsky test of motor proficiency 2 (BOT-2) (Bruininks and Bruininks 2005). The balance subset of the BOT-2 includes 9 separate tasks of which 4 are performed alternately with eyes open and eyes closed (Table 1.1). The raw score, typically the timed duration during which the child maintains position up to a maximum of 10 seconds, is converted into a point score, and the point scores for each of the 9 items are summed to produce a total point score (range 0 to 37 points). The total point score and the subject’s age at the time of testing is then used to obtain an age-matched scale score based on population norms provided by the test (range 1 to 35 units). Scores used in this study were obtained with the unilateral implant in place and functioning. Although the test provides age-matched normative scores for the balance subset, a group of normal hearing children were tested as controls to estimate the uniformity and replication of the testing environment. The test was administered by a single individual who was blinded to the results of the other vestibular tests. Testing was performed on the same day as vestibular testing in 89% of children and within a month (n=4) in the remainder.

2.5 Clinical tests of vestibular function.

Each study subject completed a battery of clinical neuro-otologic tests (Table 2.2).

<table>
<thead>
<tr>
<th>NEURO-OTOLOGIC TEST</th>
<th>FUNCTION TESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vestibulo-ocular function</strong></td>
<td></td>
</tr>
<tr>
<td>VOR Suppression</td>
<td>Visual suppression of horizontal VOR</td>
</tr>
<tr>
<td>High Acceleration Head Thrust Test (Halmagyi)</td>
<td>Unilateral horizontal canal function</td>
</tr>
<tr>
<td>Dynamic Visual Acuity</td>
<td>Bilateral horizontal VOR dysfunction leading to retinal slip</td>
</tr>
<tr>
<td>Head-shaking nystagmus</td>
<td>Symmetry of the horizontal VOR</td>
</tr>
<tr>
<td><strong>Vestibulo-spinal function</strong></td>
<td></td>
</tr>
<tr>
<td>Romberg ± vision</td>
<td>Postural stability with/ without vision</td>
</tr>
<tr>
<td>Tandem Gait</td>
<td>Postural stability</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Unterberger’s step test</td>
<td>Labyrinthine asymmetry</td>
</tr>
<tr>
<td>Dix Hallpike</td>
<td>Paroxysmal positional vertigo of posterior canal</td>
</tr>
</tbody>
</table>

Table 2.2. Standard battery of clinical neuro-otologic tests and function tested.
Results of these tests was documented and compared to both balance (BOT-2) and vestibular end organ function (i.e. calorics, VEMP and rotational chair testing). For literate children, a Sloan letters chart was used, while a LEA symbols chart was used for younger children to test dynamic visual acuity. Frenzel glasses were used to examine for post-head shake nystagmus and during the Dix-Hallpike maneuvers. Dynamic visual acuity was tested using passive head rotation at roughly 2 Hz at an amplitude of approximately 20°.

2.6 Temporal bone imaging

Pre-operative, high resolution computed tomography (CT) of the temporal bones was available for all study subjects. Pre-operative, magnetic resonance imaging (MRI) of the temporal bones and internal auditory canal was available for a proportion of study subjects (n=9/39). This imaging was performed as part of our routine evaluation prior to cochlear implantation and was obtained independent of the current study. All imaging was initially reported by two staff neuroradiologists and these reports were retrospectively reviewed by the author in an effort to define the etiology of the SNHL within our population. Where necessary the original images were reviewed again by the same two staff neuroradiologists. Serial CT imaging was available for a subset of children whose hearing loss occurred secondary to meningitis (n=6) and were being evaluated for sequential bilateral implantation as part of a separate study. All imaging was reviewed to characterize the cochleovestibular and internal auditory canal (IAC) anatomy (normal vs. abnormal) and to examine the presence and progression of ossification over the post-meningitic period of deafness (6.36 years ± 3(SD)).

2.7 Molecular genetic evaluation

One of the most prevalent genetic causes for congenital nonsyndromic SNHL is due to mutations in the GJB2 gene (Green, Mueller et al. 2003). GJB2 related deafness is inherited in an autosomal recessive fashion and mutations in this gene lead to defects in the structure and/or function of the Connexin 26 protein, a component of gap junctions, which play an important role in the maintenance of endolymphatic homeostasis (Lefebvre, Weber et al. 1990; Kikuchi, Kimura et al. 1995). Genomic DNA was tested for mutations in the GJB2 gene by direct sequence analysis of the coding region and intron/exon boundary regions in all 40 children. In the absence of mutations in the GJB2 gene, mutations in the GJB6 gene coding for Connexin 30
were also evaluated. Children with enlarged vestibular aqueducts on temporal bone imaging were also tested for mutations in the pendrin gene. The methods employed for genomic DNA extraction and mutation analysis have been described in a previous publication. (Propst, Blaser et al. 2006)

2.8 Data and Analysis

SAS v. 9.01 was used to perform all statistical analyses.

2.8.1 Tests of vestibular end organ function

Based on the criteria outlined above, VEMP, caloric-ENG and rotational chair results were categorically defined as either normal or abnormal. Horizontal canal function as assessed by caloric stimulation were further broken down into bilateral vs. unilateral loss and similarly into low and high frequency categories for rotational chair testing with the frequency cut-off set at 2 Hz. Additional analysis was also performed using the mean VOR gain in light and in dark as a continuous predictor variable. Balance ability as defined by the age standardized scale score on the balance subset of the BOT-2 was considered the dependant variable. A univariate regression analysis was performed to determine the predictive nature of vestibular end organ function measured by the available tests on balance ability estimated by BOT-2 score. A number of potential covariates were also introduced into the model (i.e. etiology of deafness, duration of implant use, progressive vs. non-progressive hearing loss, and age at implantation). Those variables that were either significant (p ≤ 0.05) or borderline significant (0.05 < p < 0.06) in the univariate analysis were then subjected to a forward stepwise multivariate regression analysis.

Comparisons of the abnormalities in vestibular end organ testing on the implanted side versus the non-implanted side were assessed using paired t-tests.

2.8.2 Clinical neuro-otologic testing

Performance on the standard battery of neuro-otologic tests (Table 2.1) was documented and compared to both static balance (BOT-2) as well as to the appropriate tests of vestibular end organ function. All clinical tests were subjectively determined by the author (SLC) to be categorically normal or abnormal. Where equivocal results were obtained the test was repeated
independently by a senior neuro-otologist at the testing facility. At the time of the clinical examination, the tester was unaware of horizontal canal and saccular function measured by caloric/rotation and VEMP testing respectively.

### 2.8.3 Static and dynamic balance

Independent student’s t-tests were used to compare balance ability estimated by the mean age-standardized scale score on the balance subset of the BOT-2 of our study population, to both the normative data provided with the test, as well as to a separate control group of children with normal development and normal hearing who were tested under the same conditions. A separate analysis was performed to attempt to quantify the relative impact of vision on balance ability in children with profound SNHL and CI. Specifically, the two skills tested both with eyes open and eyes closed (standing on one foot on a line, standing on one foot on a balance beam) were analysed separately in an attempt to tease out the relative importance of vision on balance function across the two groups, using repeated measures analysis of variance (ANOVA).
CHAPTER 3: RESULTS

When assessing the integrity of the vestibular system in children with deafness, throughout the introduction we have stressed the importance of accounting for those factors felt to influence the relationship between auditory and vestibular function. Although, one means of accomplishing this would be to study only a very specific and homogeneous patient population, this would not reflect the diverse etiologies that comprise a cross-section of children with severe to profound sensorineural hearing loss (SNHL). Instead we have chosen to examine a realistic and representative cohort of children whose SNHL is of mixed etiology and utilized all available information (imaging, molecular genetic analysis) in order to best define and account for differences due to etiology. As a result throughout each of the following section we will provide the results in the context of the group followed by a breakdown with respect to the different etiologies of which the study group is comprised.

The focus of the following section will be to describe our study findings in the context of our original research questions;

1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?
2. What influence does etiology and the onset of deafness have on this relationship?
3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?
4. Does cochlear implantation alter vestibular end organ function?

In addition, we will also discuss the correlations or lack thereof, between the different and at times overlapping measures we have chosen to quantify function of the vestibular end-organs. Likewise we will examine the influence of vision on measures of vestibular and balance function, providing a foundation for discussion regarding mechanisms for compensation in the setting of vestibular dysfunction. Finally, we will provide some specific examples of abnormalities in temporal bone anatomy as seen on imaging, to further highlight the
pathophysiology underlying the vestibular dysfunction seen in specific subgroups of our study population.

However, before moving on to describing our specific results, we feel that given the challenges inherent to any kind of testing in the pediatric population, it is important to preface our results with a description of our experience with compliance and reliability of testing in our patient population.

3.1 Compliance with testing

In our population of unilaterally implanted children, compliance with all tests was high (>88%). The youngest child for whom all testing was attempted and successfully completed was 3 years of age. Children younger than this have not yet been tested in our center, however it is certainly reasonable to attempt testing below this age, particularly using the rotational chair, and a number of centers already have considerable experience testing infants. In our study group, a single child (age=4 years) refused all 3 tests despite 2 attempts made 6 months apart. The BOT-2 could not be completed in 1 child (age = 5.6 years) due to poor attention span. Of the 36 children who completed rotational chair testing, only 2 required repeat visits (ages 4.6 and 8.2 years) and 9 children were not able to complete the test in the dark (mean age 5.1 years, ±1.15(SD)). Compliance with vestibular evoked myogenic potential testing (VEMP) was high, however concerns regarding the ability of younger children to generate the necessary baseline tonic activity in the sternocleidomastoid muscle (SCM) to obtain a reliable result arose in 6 children (mean age 4.9 years ± 1(SD)). These results were labeled indeterminate and thus not used in further analyses. Caloric testing, including ice water stimulation, when necessary, was accomplished in entirety in 28/32 (88%) children. Three of the 32 (9%) children were unable to complete all temperature trials (mean age 4.3 years ± 1(SD)). When ice water stimulation was required to try to illicit the VOR (n=9), all 9 children were able to complete the test. Only a single child (age = 17 years) experienced nausea and vomiting following caloric testing.

Given the overall high compliance and the exclusion of results that were equivocal in the case of VEMP testing, we feel confident in the accuracy of the results presented below. We will begin presenting these specific results in the following section in the context of the first experimental question:
1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?

3.2 Horizontal semicircular canal function

As outlined in the Methods (Section 2.2), horizontal semicircular canal function was measured using two modes of stimulation, caloric and rotational, the results of which are outlined below.

3.2.1 Caloric stimulation

Spontaneous nystagmus was encountered in a single subject within our study population. In this individual there was a history of congenital nystagmus. With the exception of this individual, gaze, saccadic and smooth pursuit eye movements and optokinetic nystagmus were normal in all children. Abnormalities of low frequency horizontal canal function, as measured by caloric testing, were observed in 53% (17/32) of children with a large proportion of these (6/17, 41%) reflecting mild (n=6) to moderate (n=1) unilateral abnormalities. Nine children (28%) demonstrated complete dysfunction of the horizontal canals bilaterally (areflexia) and 1 child had complete unilateral horizontal canal dysfunction. The majority of the children with bilateral horizontal canals dysfunction (areflexia) (5/9, 63%) and the single child with a complete unilateral dysfunction had acquired hearing loss secondary to meningitis. Of the remaining four children with complete bilateral horizontal canal dysfunction (areflexia), one had a cochleovestibular anomaly one had GJB2 related deafness, one had both GJB2 mutation and an abnormal labyrinth and one had hearing loss of unknown etiology with normal radiological images of the temporal bone. These results will be further broken down with respect to the various etiologies of SNHL in Section 3.6.

3.2.2 Rotational chair testing

Higher frequency horizontal canal function was also assessed by measuring the vestibuloocular reflex (VOR) during rotational chair testing. Horizontal canal dysfunction as defined by abnormalities in rotational chair testing occurred in 14/36 (39%) with the majority of affected children (10/14, 71%) having a loss of function that spanned all frequencies (0.25 to 5 Hz). Four children however had a bilateral loss of horizontal canal function that was detectable
at only higher frequencies of rotation (> 1Hz in two children and >3Hz in the remaining two). The VOR gain by frequency plot in the dark for three of these children is shown in Figure 3.1.

Overall in our study population, the incidence of horizontal canal dysfunction spanning a spectrum of severities (mild to severe, unilateral versus bilateral) in the setting of severe to profound SNHL, ranged from 39% in response to a rotational stimulus to 53% in response to a caloric stimulus.

**Figure 3.1**. VOR Gain across frequency of sinusoidal rotation in dark for 3 individual patients with loss of high frequency horizontal canal function (solid lines). Normative data and the 95% CI are also plotted (dashed line). Note the reduced gain that occurs exclusively above 3Hz in Patient 1 (●) and 3 (●●) and above 1 Hz in Patient 2 (■) signaling an isolated high frequency loss of vestibular function.

### 3.3 Saccular function

Disruption of saccular function, as measured by the absence of a VEMP response, was common in our subject population with 10/26 (38%) demonstrating an abnormality. VEMP was absent bilaterally in 5/26 (19%) and unilaterally in 5/26 (19%).
3.4 Correlation between vestibular tests

Many children with identifiable losses of horizontal canal function on caloric testing also demonstrated abnormalities on rotational chair testing and vice versa. This relationship is reflected in the moderate correlation seen between these two tests (VOR-light $F_{(1, 23)} =17.86$, $p=0.0003$, $r=0.66$; VOR-dark $F_{(1, 15)} =27.46$, $p<0.0001$, $r=0.80$) and is consistent with the fact that both are tests of horizontal semicircular canal function although over a different frequency spectrum.

In comparison, a child with an abnormality in saccular function (measured by VEMP) was not more likely to demonstrate an abnormality in horizontal canal function (measured by caloric and/or rotation chair test) as indicated by the lack of significant relationship between abnormalities of caloric or rotational chair testing and VEMP testing in our study population ($F_{(1, 27)} =8.43$, $p=0.0074$, $r=0.49$; $F_{(1, 27)} =8.43$, $p=0.0074$, $r=0.49$ respectively).

Now that we have defined the incidence of vestibular end-organ dysfunction, specifically horizontal canal and saccular dysfunction in our study population of children with severe to profound SNHL, we will follow with a description of the static and dynamic balance abilities of this same population.

3.5 Static and dynamic balance testing

Static and dynamic balance were assessed using the balance subset of the Bruininks Oseretsky test of motor proficiency 2 (BOT-2). The published age-adjusted mean (n=1520) for the BOT-2 Balance Subset is 15 ± 5 (SD) (scale range 1 to 35). In comparison, the mean performance of our control group of normal hearing children (n=19) was similar to the published norms ($μ= 17 ± 5$ (SD) units). There was no statistically significant difference between the performance of our control group and the published normative data ($t_{(18.5)} = 1.77$, $p = 0.09$). In comparison, static and dynamic balance as measured by the BOT-2 score for children wearing a cochlear implant was significantly poorer ($μ=12.9 ± 5.2$ (SD)). The difference between the performance of the implant group and both the normative and control
group was found to be statistically significant ($t_{(37.3)} = 2.98, p=0.005$; $t_{(29)} = 2.72, p=0.01$ respectively).

In summary, children with profound SNHL as a group were found to have significantly poorer performance than normal hearing children on an age-standardized test of static and dynamic balance. However, as with the specific tests of vestibular end-organ function described in the previous section, balance performance within the group spanned the entire spectrum from normal to severe dysfunction. In an effort to account for a proportion of this between subject variability, in the following section we will outline the influence of etiology on incidence of vestibular and balance function in the context of our second experimental question:

2. What influence does etiology and the onset of deafness have on the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?

3.6 Influence of etiology

3.6.1 Horizontal semicircular canal function

Horizontal canal function as assessed by caloric stimulation was most likely to be affected in children with SNHL secondary to meningitis, where all but one child (5/6) had complete bilateral loss of function. This last child demonstrated unilateral dysfunction only. Similarly horizontal canal dysfunction, defined by an abnormal VOR on rotational chair testing, occurred in the majority of children in the meningitis group (6/7). Horizontal canal dysfunction was also prevalent in the setting of abnormal cochleovestibular anomalies with 2/3 of children in this group demonstrating dysfunction on caloric testing and 3/4 displaying an abnormal VOR on rotational testing.

Thirty-six percent of the GJB2 group (4/11) had mild unilateral dysfunction all occurring on the implanted side and all had normal VOR with the exception of 2 children who demonstrated complete horizontal canal dysfunction on caloric and rotational chair testing. Those children with 35delG mutations in the GJB2 gene all demonstrated normal function or at most mild unilateral dysfunction on the implanted side. However, the 2 children with complete horizontal canal dysfunction demonstrated similar polymorphisms of the GJB2 gene (i.e.
E114G/I203T/V27I and V27I/I203T). One of these children also had abnormal cochleovestibular anatomy based on CT imaging.

In the group of children with hearing loss of unknown etiology, 36% (4/11) demonstrated horizontal canal dysfunction on caloric testing with dysfunction based on an abnormal VOR on rotational chair in 26% (4/15).

In summary, the incidence of severe horizontal canal dysfunction was highest in those with SNHL due to meningitis or a cochleovestibular anomaly compared to children with SNHL due to a GJB2 mutation or unknown etiology. For the most part, children with GJB2 related SNHL demonstrated normal horizontal canal function or at most mild dysfunction with the exception of 2 children with a different type of GJB2 mutation who demonstrated severe losses.

3.6.2 Saccular function

Saccular function was preserved based on the presence of a VEMP response in 67% of those children with SNHL due to meningitis. Of the 2 children with cochleovestibular anomalies who underwent saccular function testing, 1 demonstrated normal function while the other demonstrated an absence of function unilaterally, on the non-implanted side with the more severe anomaly on CT imaging. In children with GJB2 related deafness, saccular function was bilaterally absent in 11% (1/9), unilateral absence of saccular function was demonstrated in an additional 36% (4/11). Finally in children with SNHL of unknown etiology, saccular function was absent bilaterally in 25% (2/8).

Overall, saccular dysfunction was absent in nearly half the children with abnormal cochleovestibular anatomy and GJB2 related deafness while 1/3 or less of children with SNHL due to meningitis or unknown causes demonstrated saccular dysfunction on VEMP testing.

3.6.3 Static and dynamic balance

As was the case with vestibular end-organ function, static and dynamic balance ability as approximated by BOT-2 score, also varied significantly according to etiology. Children whose hearing loss was attributed to meningitis had the worst balance abilities reflected by the poorest scores on the BOT-2 (μ=8 ± 5.0(SD)) followed by those with abnormal cochleovestibular anatomy (μ=9 ± 1.9(SD)), hearing loss of unknown etiology (μ=14.1 ± 4.8(SD)) and finally
GJB2 related deafness ($\mu=15.6 \pm 5.5$ (SD)). Differences in the balance abilities, represented by mean BOT-2 performance, of children with meningitis compared to those with GJB2 deafness as well as that of children with abnormal cochleovestibular anatomy compared to those with GJB2 related deafness were found to be statistically significant. No significant differences were however seen in comparing the performance of children with deafness due to meningitis vs. abnormal cochleovestibular anatomy or hearing loss of unknown etiology. All comparisons were made using a one-way ANOVA and Bonferroni correction for the multiple comparisons with a significance level of 5% (Table 3.1).

In summary, mean static and dynamic balance abilities were poorest in children with SNHL due to meningitis and cochleovestibular anomalies and best in children with GJB2 related deafness or SNHL of unknown etiology.

In the previous section we have separately examined vestibular end-organ function (i.e. horizontal canal and saccular function) and balance function in our study population of children with severe to profound SNHL. We know however that input from the peripheral vestibular system is one of several factors that contribute to the maintenance of static and dynamic balance. With this in mind the following section will address our third experimental question:

3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?

### 3.7 Correlation between vestibular end-organ function and balance ability

<table>
<thead>
<tr>
<th>Comparisons of Etiology</th>
<th>Difference of Means</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GJB2 – Unknown</td>
<td>2.83</td>
<td>-2.13 – 7.80</td>
</tr>
<tr>
<td>GJB2 – Abnormal Cochlea</td>
<td>7.50 *</td>
<td>0.84 - 14.15*</td>
</tr>
<tr>
<td>GJB2 - Meningitis</td>
<td>8.50 *</td>
<td>2.22 – 14.78*</td>
</tr>
<tr>
<td>Unknown – Abnormal Cochlea</td>
<td>4.67</td>
<td>-1.61 – 10.94</td>
</tr>
<tr>
<td>Unknown - Meningitis</td>
<td>5.67</td>
<td>-0.21 – 11.54</td>
</tr>
<tr>
<td>Abnormal Cochlea - Meningitis</td>
<td>1.0</td>
<td>-6.36 – 8.36</td>
</tr>
</tbody>
</table>

**Table 3.1.** One-way analysis of variance testing the effect of etiology on performance on the BOT-2. Critical t-value = 2.8. CI = confidence interval. * denotes significance.
In Figure 3.2, balance ability, represented by the BOT-2 score, is plotted according to horizontal canal and saccular function as defined by the categorical results of the vestibular tests (normal vs. abnormal rotational chair and VEMP; normal vs. abnormal (unilateral vs. bilateral)).

**Figure 3.2.** Age standardized score on balance subset of BOT-2 against results of rotational chair testing (A), caloric-ENG testing (B) and VEMP testing (C). ( ■ Mean ± 1 Standard deviation).
caloric results). There is considerable spread in performance but the mean difference is largest when balance ability is grouped according to horizontal canal function assessed by rotational chair testing. Specifically, horizontal canal function as measured by a rotational stimulus, correlated significantly with balance ability estimated by BOT-2 performance (p=0.0036; r=0.49).

Given that horizontal canal function in response to rotation was measured both in the light and dark, linear regression analyses were repeated using the mean VOR gain in light and in dark as predictor variables. As detailed in Table 3.2, the correlation between balance function measured by the BOT-2 score and horizontal canal function based on the results of rotational chair testing remained significant regardless of whether the rotational chair results were defined categorically (normal vs. abnormal) or continuously (mean VOR gain in light and in dark). Given that 4 children demonstrated normal gains at low frequencies of rotation, with abnormal gain at high frequencies or rotation (Figure 3.1), a subanalysis was consequently performed to assess whether or not the correlation between balance ability and horizontal canal function was different at low versus high frequency. In this analysis, rotational chair results were defined both categorically (normal vs. abnormal) and continuously (mean gain VVOR and VORD). Linear regression analyses revealed that horizontal canal function during rotational chair testing, correlated well with balance function measured by BOT-2 scores at both high and low

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>n</th>
<th>Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>CHAIR – Categorical all frequencies</td>
<td>32</td>
<td>0.006*</td>
</tr>
<tr>
<td>Mean VVOR gain all frequencies</td>
<td>31</td>
<td>0.01*</td>
</tr>
<tr>
<td>Mean VORD gain all frequencies</td>
<td>24</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Table 3.2. Analysis of rotational chair test results as a categorical vs. continuous variable predictor of BOT-2 Score. * denotes significance at p=0.05 level.
frequencies of rotations when the test results were categorical (Table 3.3). This relationship was likewise preserved for mean VOR gain in the dark at both low (≤2Hz) and high (>2Hz) frequency. However while, the mean VOR gain in the light was strongly correlated with balance ability approximated by score on the BOT-2 at high frequency (>2Hz), it was no longer a good correlate at low frequency (≤ 2Hz) (Table 3.3).

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>n</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>Correlation coefficient (r)</td>
</tr>
<tr>
<td>CHAIR – Categorical Low Frequencies</td>
<td>32</td>
<td>0.0001*</td>
<td>0.63</td>
</tr>
<tr>
<td>CHAIR – Categorical High Frequencies</td>
<td>32</td>
<td>0.006*</td>
<td>0.48</td>
</tr>
<tr>
<td>VVOR - ≤2Hz</td>
<td>31</td>
<td>0.33</td>
<td>0.18</td>
</tr>
<tr>
<td>VVOR - &gt;2Hz</td>
<td>31</td>
<td>0.01*</td>
<td>0.46</td>
</tr>
<tr>
<td>VORD - ≤2Hz</td>
<td>24</td>
<td>0.01*</td>
<td>0.50</td>
</tr>
<tr>
<td>VORD - &gt;2Hz</td>
<td>24</td>
<td>0.02*</td>
<td>0.47</td>
</tr>
</tbody>
</table>

**Table 3.3.** Predictive ability of the mean VOR gain in light and dark for BOT-2 score at low (≤2 Hz) and high frequencies (> 2 Hz).

Abnormalities of low frequency horizontal canal function, as measured by caloric testing, correlated well with balance ability approximated by BOT-2 results (β=7.90, SE=2.07, p=0.0008, r = 0.71). However, saccular dysfunction, assessed by VEMP testing, was not correlated with balance ability (p=0.88; r=0.03). Figure 3.2 plots and highlights the relationship between static and dynamic ability and abnormalities of low frequency horizontal canal function and saccular function respectively.

In an effort to control for potentially confounding factors related to the demographics of our study population, additional variables were examined in our univariate analysis (Table 3.4). These included etiology of deafness, age and duration of implantation, nature of the hearing loss (progressive vs. non-progressive) and type of rotational chair paradigm used (pseudorandom vs. sinusoidal). Age at testing was not considered in the analysis given that BOT-2 scores are age standardized and our previous study demonstrated that this relationship holds across a spectrum of ages and performance (Cushing SL 2007).
In Figure 3.3, balance ability, approximated by BOT-2 performance, is plotted against age at implantation and duration of implant use. The considerable variability in balance ability across our study population is readily apparent in these plots. While the age at which a child is implanted does not significantly affect his/her performance on the BOT-2 (p=0.46, r=0.13), a longer duration of implantation appears to predict significantly poorer balance performance (BOT-2 score) (p=0.015, r=0.4) on univariate analysis.

<table>
<thead>
<tr>
<th>Effect</th>
<th>F-value</th>
<th>$DF_{(num., denom.)}$</th>
<th>Slope</th>
<th>Standard Error</th>
<th>Correlation coefficient (r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEMP</td>
<td>0.02</td>
<td>1, 20</td>
<td>0.34</td>
<td>2.33</td>
<td>0.033</td>
<td>0.88</td>
</tr>
<tr>
<td>Caloric</td>
<td>10.37</td>
<td>2, 20</td>
<td>-7.91</td>
<td>2.01</td>
<td>0.72</td>
<td>0.0008*</td>
</tr>
<tr>
<td>VOR- light</td>
<td>7.46</td>
<td>1, 29</td>
<td>14.80</td>
<td>5.42</td>
<td>0.45</td>
<td>0.01*</td>
</tr>
<tr>
<td>VOR - dark</td>
<td>10.13</td>
<td>1, 23</td>
<td>10.45</td>
<td>3.28</td>
<td>0.56</td>
<td>0.004*</td>
</tr>
<tr>
<td>Etiology</td>
<td>6.40</td>
<td>3, 32</td>
<td>7.50</td>
<td>2.37</td>
<td>0.61</td>
<td>0.002*</td>
</tr>
<tr>
<td>Duration of Implant Use</td>
<td>6.58</td>
<td>1, 34</td>
<td>-0.77</td>
<td>0.30</td>
<td>0.40</td>
<td>0.01*</td>
</tr>
<tr>
<td>Age at Implantation</td>
<td>0.56</td>
<td>1, 34</td>
<td>0.18</td>
<td>0.24</td>
<td>0.13</td>
<td>0.46</td>
</tr>
<tr>
<td>Progressive vs. non-progressive SNHL</td>
<td>3.83</td>
<td>1, 34</td>
<td>5.22</td>
<td>2.67</td>
<td>0.32</td>
<td>0.059</td>
</tr>
<tr>
<td>Test Type</td>
<td>0.49</td>
<td>1, 32</td>
<td>1.84</td>
<td>2.63</td>
<td>0.13</td>
<td>0.49</td>
</tr>
</tbody>
</table>

**Table 3.4.** Univariate linear regression analysis of factors influencing standardized score on balance subset of BOT-2, a test of static and dynamic balance. * denotes significance at p=0.05 level. DF = degrees of freedom.
Figure 3.3. Age standardized score on balance subset of BOT-2 plotted by age at implantation (A) and duration of implant use (B). Univariate linear regression equation and $R^2$ shown on graph. ♦ unknown □ connexin-26 ▲ meningitis ● abnormal cochlea.
Balance ability, as measured by BOT-2 score, is plotted according to etiology and onset of deafness (progressive vs. non-progressive) in Figure 3.4. In this plot, balance ability tends to cluster according to the etiology of their deafness. Those children with meningitis or cochleovestibular anomalies displayed poorer balance performance than their counterparts with

![BOT-2 Score by Etiology](image)

**Figure 3.4.** Age standardized score on balance subset of BOT-2 plotted by etiology (A) and type of hearing loss (progressive vs. non-progressive) (B). (■ Mean ± 1 Standard deviation).
GJB2 related deafness or hearing loss of unknown etiology, although the latter two groups also contained a number of poor performers. The differences in balance abilities and scores across etiology are reflected in the significance of etiology as a predictor of balance function, measured by BOT-2 score, on univariate analysis (p=0.002, r=0.61). Only 4 children in our study had a progressive SNHL and figure 3.4B demonstrates that 3 of these 4 children had very good static and dynamic balance as reflected by their high BOT-2 scores, while 1 child with a progressive loss performed quite poorly.

Given this variability and small sample size, nature of the hearing loss (progressive vs. non-progressive) approached but did not reach statistical significance in univariate analysis (p=0.06, r=0.32) (Table 3.3).

In summary, univariate regression analysis indicated that horizontal canal function as measured by either rotational or caloric stimulus, correlated well with balance ability, as approximated by BOT-2 score. Balance ability was also significantly correlated with the etiology and duration of implant use on univariate analysis. In addition, the correlation between balance ability and onset of deafness (progressive vs. non-progressive) was only marginally non-significant. Likely many of the variables found to be significant in the univariate analysis are interrelated. In order to determine their independent influence of each of the variables in our regression model, variables found to be significantly correlated with balance ability as measured by BOT-2 score were introduced into a multivariate regression model. Prior to proceeding with a multivariate regression however, we must remember that a significant, although not absolute, correlation exists between rotational chair testing and caloric testing as discussed in Section 3.4. Given this strong correlation, entering both parameters, horizontal canal function in response to rotation and caloric stimulation, into the regression analysis leads to a loss of significance of all variables in question. Therefore our multivariate regression analysis was conducted for 3 separate models, each of which includes a different but correlated measure of horizontal canal function, notably: 1) rotational chair testing in light; 2) rotational chair testing in dark; and 3) caloric testing.

Results of the multivariate regression analysis are shown in Table 3.5. Controlling for the effects of the additional variables, the p-values related to the slope of each parameter
remained largely unchanged from those obtained on univariate analyses. In this analysis, horizontal canal function as measured by mean VOR gain for rotational chair testing in dark remained the most significant and robust correlate of balance ability, approximated by the BOT-2 score (p=0.005, multiple R = 0.78) followed by rotational chair testing in light (p=0.02, multiple R = 0.70) and finally caloric testing (p=0.03, multiple R = 0.64). The nature of the hearing loss (progressive vs. non-progressive) remained a significant correlate of balance ability in the models that contained mean VOR gain in light and in dark (light: p=0.006, multiple R = 0.70; dark: p=0.04, multiple R = 0.78) but not in the analysis of caloric testing (p=0.20, multiple R = 0.64) as the measure of horizontal canal function. Neither etiology of deafness nor duration of implant use were significantly correlated with balance function as estimated by BOT-2 score in any of the multivariate regression models (Table 3.5).

The best fit regression model (R=0.77) contained a measure of horizontal canal function, mean VOR gain in dark, as well as etiology and onset of hearing loss (progressive vs. non-progressive). Specific statistics for each of the parameters in this analysis are provided in Table 3.6.

In summary, in children with severe to profound SNHL, a strong relationship exists between their static and dynamic balance ability, as measured by BOT-2 score, and the function of their horizontal semicircular canals particularly when it is measured by the mean VOR gain in the dark in response to a rotational stimulus. Furthermore, the etiology and onset of hearing loss appear to significantly modulate this relationship.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F-value</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td></td>
</tr>
<tr>
<td>VOR - light</td>
<td>6.71</td>
</tr>
<tr>
<td>Etiology</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of Implant Use</td>
<td>0.78</td>
</tr>
<tr>
<td>Type of Hearing loss (progressive vs. non-progressive)</td>
<td>8.88</td>
</tr>
<tr>
<td><strong>Dark</strong></td>
<td></td>
</tr>
<tr>
<td>VOR - dark</td>
<td>9.97</td>
</tr>
<tr>
<td>Etiology</td>
<td>1.64</td>
</tr>
<tr>
<td>Duration of Implant Use</td>
<td>0.76</td>
</tr>
<tr>
<td>Type of Hearing loss (progressive vs. non-progressive)</td>
<td>5.04</td>
</tr>
<tr>
<td><strong>Caloric Testing</strong></td>
<td></td>
</tr>
<tr>
<td>Caloric Testing</td>
<td>5.54</td>
</tr>
<tr>
<td>Etiology</td>
<td>1.59</td>
</tr>
<tr>
<td>Duration of Implant Use</td>
<td>0.33</td>
</tr>
<tr>
<td>Type of Hearing loss (progressive vs. non-progressive)</td>
<td>1.79</td>
</tr>
</tbody>
</table>

**Table 3.5.** Multivariate analysis with 3 separate tests of lateral canal function as main predictor variables. * denotes significance at p=0.05 level.

<table>
<thead>
<tr>
<th>Effect</th>
<th>F-value</th>
<th>DF(num., denom.)</th>
<th>Slope</th>
<th>Standard Error</th>
<th>Multiple R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOR - dark</td>
<td>11.41</td>
<td>3, 23</td>
<td>9.22</td>
<td>2.73</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>1.79</td>
<td>3, 23</td>
<td>8.00</td>
<td>0.97</td>
<td>0.0053*</td>
<td></td>
</tr>
<tr>
<td>Progressive vs. non-progressive SNHL</td>
<td>9.79</td>
<td>3, 23</td>
<td>1.31</td>
<td>2.56</td>
<td>0.77</td>
<td>0.1955</td>
</tr>
</tbody>
</table>

**Table 3.6.** Best fit linear regression model. * denotes significance at p=0.05 level. DF = degrees of freedom.
3.8 Clinical evaluation of vestibular function

In addition to having undergone rotational chair, caloric and VEMP testing in order to evaluate vestibular end-organ function, all children were also assessed using a traditional battery of clinical tests. Of the clinical neuro-otologic battery used to examine our subjects (Table 3.6), abnormal results were found only on those tests assessing high frequency horizontal canal function, notably the head thrust and dynamic visual acuity (DVA) testing. Of the 13 children with bilateral horizontal canal dysfunction represented by abnormal rotational chair test results who underwent a clinical head thrust test, 5 (38%) demonstrated corrective saccades with head rotation to either side suggesting bilateral abnormalities. None of the children with unilateral horizontal canal losses (n=7) had an abnormal head thrust test result. Of the 11 children with bilateral horizontal canal dysfunction represented by abnormal rotational chair test results who also completed DVA testing, 8 had abnormal DVA findings. In a single child, DVA testing suggested a bilateral horizontal canal deficit as the child significantly regressed (6 lines) in their ability to clearly read the eye chart during high frequency head rotation, however rotational chair test result did not confirm the presence of such a deficit. There was a moderate correlation between the head thrust test and the caloric as well as rotational chair results (calorics: $\beta=1.19$, SE=0.37, $p=0.003$, $r = 0.53$; VOR light: $\beta=0.31$, SE=0.09, $p=0.002$, $r = 0.59$; VOR dark: $\beta=0.63$, SE=0.18, $p=0.003$, $r = 0.69$). A stronger correlation existed between the presence of oscillopsia found in DVA testing and an abnormal rotational chair test result (VOR light; $\beta=0.24$, SE=0.06, $p=.0007$, $r = 0.66$; VOR dark: $\beta=0.51$, SE=0.14, $p=0.003$, $r = 0.70$). If the caloric test result is considered the gold standard tool to detect horizontal canal dysfunction, the sensitivity of the head thrust manoeuvre was 29% (4/14) and its specificity was 100% (15/15) (no false positives were identified). Similarly, the sensitivity and specificity of DVA testing was 73% (8/11) and 93% (14/15), respectively based on a gold standard of rotational chair testing in light.

Overall, few abnormalities in peripheral vestibular and balance function were noted using a standard battery of clinical tests. The high frequency head thrust and dynamic visual acuity both of which measure high frequency horizontal canal function in a unilateral and bilateral fashion respectively, were those that detected the highest proportion of abnormalities of horizontal canal function. In keeping with this, the high frequency head thrust and dynamic
visual acuity test were well correlated with horizontal canal function assessed using either a rotational or caloric stimulus.

This completes our assessment of peripheral vestibular and balance function in our study population. In the following section we will begin to examine differences in peripheral vestibular function as they may relate to cochlear implantation, keeping in mind our fourth and final experimental question:

4. Does cochlear implantation alter vestibular end organ function?

### 3.9 Impact of Implantation

Although not an ideal model, vestibular assessment in children with unilateral implants does afford a means of testing the impact of implantation by examining side differences in vestibular end organ function. For those children undergoing sinusoidal rotation, a paired comparison of the VOR gain in light and dark on the implanted side (light \(\mu=0.90 \pm 0.28\) (SD); dark \(\mu=0.79 \pm 0.41\) (SD)) versus the non-implanted side (light \(\mu=0.921 \pm 0.29\) (SD); dark \(\mu=0.86 \pm 0.58\) (SD)) was performed. No significant difference existed between horizontal canal function as assessed by individual VOR gains on the implanted side versus those on the non-implanted side in either light or dark using a paired analysis across frequencies (Table 3.7). Although the difference between horizontal canal function at 3Hz as measured by VOR in the dark appeared

<table>
<thead>
<tr>
<th>Frequency</th>
<th>light</th>
<th>dark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DF</td>
<td>t(DF)</td>
</tr>
<tr>
<td>0.25</td>
<td>27</td>
<td>0.81</td>
</tr>
<tr>
<td>0.5</td>
<td>27</td>
<td>0.39</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>1.29</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>1.73</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Table 3.7.* Results of paired t-test for mean VOR gain in non-implanted ear vs. implanted ear across frequencies in light and in dark. * denotes significance at p=0.05 level. DF = degrees of freedom. Bonferroni adjusted level of significance 0.007.
significant \((t_{23} = 2.26, p=0.03)\), this did not remain significant once levels were adjusted for multiple comparison (Bonferroni adjusted level of significance 0.004).

In many of the children with unilateral horizontal canal hypofunction on caloric testing \((n=7)\), the implanted ear was the affected ear \((71\% \ (5/7))\). This difference however did not reach statistical significance (paired t-test: \(t_{30}=1.44, p = 0.16\)). Similarly, in those children with unilateral abnormalities in saccular function, the VEMP was absent on the implanted side in 3/5 \((60\%)\). The difference between saccular function on the implanted versus the non-implanted side was likewise not statistically significant (paired t-test: \(t_{22}=1.37, p=0.19\)).

Of the nearly 600 patients implanted at the Hospital for Sick Children, clinically observed dizziness indicative of vestibular dysfunction has occurred only in roughly 1\% of implanted patients \((n=7)\). In all patients, this has occurred either immediately or within several days following surgery. In all cases the history of the disturbance has been compatible with a peripheral disorder and the disturbance resolved over the period of one to two weeks at which point they then resumed normal activity. In the 40 children that were part of the current study, two subjects described such a history. Although many years had passed since the time of initial implantation, calorics were normal in both children at the time of testing. Only one underwent rotational chair testing and this again was normal. Interestingly, one of these children required re-implantation over the course of the study and again experienced quite disabling symptoms of a peripheral vestibular event subsequent to re-implantation which again resolved. Follow-up caloric and rotational chair testing 6 months following re-implantation has again revealed recovery of normal function.

In summary, no significant side differences were detected in horizontal canal function, as assessed by either a caloric or rotational stimulus, or in saccular function, as measured by VEMP testing. There was however a trend towards an increased incidence of saccular dysfunction and mild unilateral horizontal canal dysfunction measured by a caloric stimulus in the implanted ear. The current study paradigm did not allow us to assess the impact of implantation on balance function as all children had a unilateral implant at the time of testing. What can be said is that all children in the study were ambulatory and participated in a variety of activities that challenged balance (i.e. bicycling, swimming, horseback riding etc) some of them
despite severe bilateral horizontal canal dysfunction. While we have previously indicated that peripheral vestibular input is one component in the maintenance of balance, inputs from other systems including the visual and somatosensory systems also play a role. In the following section, we will examine the impact of vision in the compensation of bilateral vestibular loss as well as on balance performance.

3.10 Impact of vision on vestibular and balance function

Given the importance of visual cues to the VOR and the maintenance of dynamic balance, a secondary analysis was performed to try and isolate the impact of vision on both tests of balance and vestibular end organ function. A number of children completed rotational chair testing in both light and in dark. This provided an opportunity to examine the effects of vision on the mean VOR gain across frequencies. Even a child with complete bilateral horizontal canal dysfunction (areflexia) may be able to compensate for this loss using vision in the rotational chair paradigm in light, particularly at low frequency. However, this same child may demonstrate an uncompensated loss at higher frequencies of rotation and in the dark. A paired analysis across frequencies was therefore performed (Table 3.8) and did not demonstrate any significant difference between the VOR gain in light and in dark across the frequencies (Figure 3.5).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>DF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>26</td>
<td>0.24</td>
</tr>
<tr>
<td>≤ 2 Hz</td>
<td>26</td>
<td>0.95</td>
</tr>
<tr>
<td>&gt; 2 Hz</td>
<td>26</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 3.8. Difference of mean VOR gain in light vs. dark. Bonferroni adjusted level of significance 0.01.
Figure 3.5. Age standardized score on balance subset of BOT-2 plotted by mean VOR gain in light (VVOR - left column) and dark (VORD - right column) for all frequencies of rotation (top row), low frequencies of rotation (≤2 Hz) (middle row) and high frequencies of rotation (bottom row). ▲ unknown  ■ connexin-26  ▲ meningitis  ● abnormal cochlea.
Given the expected differences in light and in dark for children with significant losses of horizontal canal function as indicated by decreased VOR gain during rotation, a second sub-analysis was performed including only those 13 subjects who demonstrated abnormal horizontal canal function based on the results of rotational chair testing and, as detailed in Table 3.9, a significant difference was found between the mean VOR gain in light versus in dark. This relationship held statistically regardless of whether mean gain across all frequencies or the mean gain for low frequency rotation (≤2Hz) was used, however, no significant difference in mean gain for VOR in light versus dark occurred at high frequency (>2Hz). This relationship held also when corrected for multiple comparisons (Bonferroni adjusted level of significance = 0.01) (Table 3.9, Figure 3.6).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>DF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11</td>
<td>0.0006*</td>
</tr>
<tr>
<td>≤ 2 Hz</td>
<td>11</td>
<td>0.0008*</td>
</tr>
<tr>
<td>&gt; 2 Hz</td>
<td>11</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Table 3.9.** Difference of mean VOR gain in light vs. dark for subjects with categorically abnormal rotational test results. * denotes significance at Bonferroni adjusted level of 0.01.

A similar attempt was made to quantify the impact of vision on the static and dynamic balance as measured by the BOT-2. One of the items on the BOT-2 is standing on one foot for a period of 10 seconds. This task is repeated with 4 permutations (i.e. ± vision, ± balance beam) allowing us to assess the relative contribution of vision on static balance performed under easy (standing on one foot) and more difficult (standing on one foot on a balance beam) conditions. Not surprisingly, large decrements in performance occur when vision is removed for both normal hearing children and children with SNHL and CI. The impact of vision on performance across the two groups is graphically depicted in Figure 3.7.

This difference in performance eyes open versus eyes closed was supported statistically on repeated measures ANOVA (normal hearing: p=0.0003; SNHL and CI p<0.0001) (Table 3.10). Performance also worsened in all children with the addition of a balance beam although the magnitude of this difference was smaller (normal hearing: p=0.004; SNHL and CI: p=0.01). Although as a group, children with SNHL and CI start out with lower overall scores, the rate of decrement in performance when the eyes are closed is the same in both groups as illustrated by the nearly parallel slopes across these two groups displayed in Figure 3.8. This relationship holds for both the easy and difficult task (Figure 3.8).
Figure 3.6. Age standardized score on balance subset of BOT-2 for children with VOR abnormalities on rotational chair testing plotted by mean VOR gain in light (VVOR - left column) and dark (VORD - right column) for all frequencies of rotation (top row), low frequencies of rotation (≤ 2 Hz) (middle row) and high frequencies of rotation (bottom row). • unknown ■ connexin-26 ▲ meningitis ● abnormal cochlea.
This finding is supported statistically by the presence of a non-significant interaction between vision and group ($F_{(1,50)} = 1.27$, $p=0.27$). However it is important to remember that the performance of our implant population on these balance tasks spanned the entire range of above average to well below average and some of these children had known dysfunction of their vestibular end organs while others did not. In order to ensure that the results regarding the reliance of deaf children on vision were not masked by the heterogeneity in performance and peripheral vestibular function across our study population, we separated out those children with SNHL and CI who demonstrated dysfunction of horizontal canal as indicated by abnormalities on rotational chair testing and thus for the most part had the poorest balance ability and scores on the BOT-2. If an overreliance on vision exists, it would be most likely detected in comparing the poorest performers to the control group. However, even in this subgroup comparison, the rate of change in performance with their eyes closed was equal between the control group and the children with peripheral vestibular dysfunction demonstrated on rotational chair testing. This was supported statistically by an absence of a significant difference existed between the slopes of the control and subgroup of CI subjects captured by the non-significant vision*group interaction term ($F_{(1,30)} = 1.67$, $p=0.2061$) (Table 3.11).

<table>
<thead>
<tr>
<th>Effect</th>
<th>F value</th>
<th>DF (model, residual)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>15.68</td>
<td>1,50</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Balance Beam (present vs. absent)</td>
<td>39.82</td>
<td>1,50</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Balance Beam * Group</td>
<td>0.21</td>
<td>1,50</td>
<td>0.65</td>
</tr>
<tr>
<td>Eyes (open vs. closed)</td>
<td>69.02</td>
<td>1,50</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Eyes * Group</td>
<td>1.27</td>
<td>1,50</td>
<td>0.27</td>
</tr>
<tr>
<td>Balance Beam * Eyes</td>
<td>2.58</td>
<td>1,50</td>
<td>0.11</td>
</tr>
<tr>
<td>Balance Beam * Eyes * Group</td>
<td>0.65</td>
<td>1,50</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Table 3.10. Repeated measures ANOVA examining the impact of vision on one item of the BOT-2 (Standing on one foot, on and off a balance beam). * denotes significance at $p=0.05$ level. DF = degrees of freedom.
Figure 3.7. Mean duration (±1 SE) of posture maintenance (maximum = 10 seconds) while standing on one foot with eyes opened and closed while standing on a balance beam (B) and off a balance beam (A) for normal hearing children (◆), children with profound SNHL and unilateral CI (■) and children with SNHL, unilateral CI and abnormal VOR on rotational chair testing (▲).
In summary, children with bilateral loss of horizontal canal function, were able to use their vision to maintain target fixation during rotation, particularly at frequencies less than 2 Hz. In contrast, in this same group, while balance ability with their eyes open was better than with eyes closed, the decrement in performance without vision was similar in proportion to both children with normal horizontal canal function with and without SNHL.

### 3.1 Temporal bone imaging

In section 3.6 we underlined that differences in vestibular end-organ and balance function exists when we account for the influence of the etiology of the SNHL. In some cases such as meningitis and congenital cochleovestibular anomalies, the etiology is reflected in the imaging of the temporal bone. For this reason we reviewed all pre and post-operative imaging was undertaken in order to identify any anatomic correlates for the results obtain on both vestibular end organ and static and dynamic balance testing. In this final section we will define the incidence of radiologic abnormalities in our study group and demonstrate the typical radiologic features associated with several of the specific etiologies represented. Figure 3.8 demonstrates the normal appearance of the vestibular end organs on a high resolution axial scan of the temporal bone.

<table>
<thead>
<tr>
<th>Effect</th>
<th>F value</th>
<th>DF (model, residual)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>20.67</td>
<td>1, 30</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Balance Beam (present vs. absent)</td>
<td>17.31</td>
<td>1, 30</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Balance Beam * Group</td>
<td>1.26</td>
<td>1, 30</td>
<td>0.27</td>
</tr>
<tr>
<td>Eyes (open vs. closed)</td>
<td>42.05</td>
<td>1, 30</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Eyes * Group</td>
<td>1.67</td>
<td>1, 30</td>
<td>0.21</td>
</tr>
<tr>
<td>Balance Beam * Eyes</td>
<td>0.76</td>
<td>1, 30</td>
<td>0.39</td>
</tr>
<tr>
<td>Balance Beam * Eyes * Group</td>
<td>1.52</td>
<td>1, 30</td>
<td>0.23</td>
</tr>
</tbody>
</table>

**Table 3.11.** Repeated measures ANOVA examining the impact of vision on one item of the BOT-2 (Standing on one foot on and off a balance beam) in subjects with abnormal rotational chair testing. * denotes significance at p=0.05 level. DF = degrees of freedom.
Figure 3.8. High resolution non-enhanced computed tomography (NECT) of a normal temporal bone (A, B) demonstrating axial sections through the horizontal semicircular canal at the level of the cochlea (A) and the internal auditory canal (IAC).

The majority of patients had normal findings on CT and MRI of the temporal bones and IAC (28/40; 70%). However all children with meningitis demonstrated some degree of ossification seen on CT scan both pre-operatively and post-operatively. One example of this shown in figure 3.10, this was representative of the majority of these children, as ossification had progressed significantly in the inter-scan interval (ISI) (μ=6.4 years ±3.0 (SD)), although ossification remained stable in one child (ISI=4.87 years) (Figure 3.9).
Figure 3.9. High resolution NECT of left temporal bone in a child with acquired meningitis. Axial section through posterior semicircular canal with arrow denoting left anterior portion of the horizontal canal (A, C). Axial section through horizontal semicircular canal with arrow denoting superior portion of the posterior canals (C, D) Images in A and B obtained several weeks following acute bacterial meningitis. Follow-up images (C and D) were obtained at 10 years and demonstrate bony obliteration of both the horizontal (C) and posterior (D) canals.
The semicircular canals were more commonly and more severely affected than the vestibular or the cochlea, with the lateral canal appearing to be the most likely to demonstrate ossify as demonstrated in Figure 3.10. All but one child with meningitis who had repeat CT imaging demonstrated bilateral areflexia on caloric examination. A single patient unilateral osseous obliteration of the labyrinth had occurred without any history suggestive of labyrinthitis, meningitis or trauma (Figure 3.11).

**Figure 3.10.** 5 year follow-up, high resolution NECT of right temporal bone in a child with acquired meningitis. A – Axial section through cochlea, note lack of cochlear involvement. B – Axial section through horizontal semicircular canal with arrow denoting ossification at the apex of the horizontal canal. C – Axial section through posterior semicircular canal with arrow denoting open lumen of posterior canal with no sign of ossification. D – Axial section through superior semicircular canal with arrow denoting open lumen of superior canal with no sign of ossification.
Horizontal canal function measured by rotational chair testing revealed a mild bilateral high frequency vestibular loss with VOR gains in the affected ear (R) being slightly lower than in the unaffected ear. Unfortunately caloric studies were not performed in this child. Figure 3.12 shows results from one child with abnormal anatomy, the scan shows a severely hypoplastic vestibule and complete absence of semi-circular canals, these inner ear findings are very typical for children with CHARGE syndrome. As expected this child demonstrated bilateral loss of horizontal canal function (areflexia) on caloric and rotational chair testing. Saccular function was preserved in this child as suggested by bilateral preservation of the VEMP response.

This section completes the presentation of our study results. In the following chapter we will move on to a discussion of these results as they relate to defining the relationship between sensorineural hearing loss and vestibular and balance function in children with unilateral cochlear implants. We will emphasize how our findings relate and contribute to the current literature on this topic.
Figure 3.12. High resolution NECT of the temporal bone of a child with features of CHARGE association (A, B). Arrows denotes severe left sided vestibular hypoplasia with rudimentary anlage in the usual location of the horizontal semicircular canals at the level of the cochlea (A) and the IAC (B).
CHAPTER 4: DISCUSSION

Identifying a peripheral vestibular loss or balance dysfunction in a child can be difficult for a number of reasons. The primary challenge lies in ensuring compliance with testing protocols. In the setting of SNHL these compliance issues become even more difficult given the added communication barriers. The ability to effectively convey verbal reinforcement is a hallmark in the success of pediatric testing and this is compromised in children who have delayed oral speech-language development resulting from hearing loss. Secondly, while the functional sequelae of a dysfunction of sensory integration (as defined in section 1.7.4) may be easily identified, that of a pure and isolated peripheral vestibular dysfunction may be more elusive (Rapin 1974). The identification of vestibular losses, particularly in children, require not only tests of balance function that attempt to isolate the contribution of the vestibular end organs by removing or distorting other sensory inputs, but also requires that the tasks be sufficiently difficult. This is highlighted by the fact that a bilateral vestibular loss can be missed using a standard test of static balance such as the Romberg test or measuring postural sway even with the eyes closed (Brookhouser, Cyr et al. 1982; Horak, Shumway-Cook et al. 1988). Finally, a much more difficult issue to resolve, is that current mainstream tests of peripheral vestibular function provide a limited assessment of a subset of the vestibular end organs, in particular the horizontal canal and the saccule.

Keeping in mind the challenges of identifying peripheral vestibular and balance dysfunction in children with SNHL, we will begin our discussion by addressing compliance and reliability of vestibular testing in children. We will then move on to the interpretation of our results with the aim of addressing and answering our outlined research questions notably:

1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?
2. What influence does etiology and time course of an inner ear injury have on this relationship?
3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?
4. Does cochlear implantation alter vestibular end organ function?

Subsequently, we will speculate as to the mechanisms and strategies that children with congenital or early onset vestibular dysfunction may employ to compensate for their loss of function. Finally we will discuss the clinical relevance of our findings, followed by an outline of potential directions for future investigations.

4.1 Compliance with Testing

Specifically, overall compliance with testing was high although the youngest child in whom we attempted testing was 3 years of age. This high degree of compliance however somewhat underestimates the challenges involved in testing this population and the time commitment for testing and re-testing that was necessary to achieve reliable results. We have certainly made many small but important adjustments in our testing centre and protocols to accommodate paediatric patients and continue to do so as we accumulate experience. To our advantage, all children participating in the study had unilateral cochlear implants which were left in place wherever possible and appropriate. Although there is some redundancy in using both caloric and rotational chair testing, this redundancy was useful in that inconsistencies between these two tests helped identify situations in which repeat evaluation would be useful. Proper assessment of the vestibular evoked myogenic potential (VEMP) was questionable in a number of our younger study participants. Specifically, the absence of a myogenic response in this group may have been related to an inability to produce sufficient and consistent tonic activation of the sternocleidomastoid muscle (SCM) to allow for replication during averaging. Therefore, the yield on VEMP testing was much lower given the exclusion of cases where tonic muscle activation was felt to be insufficient. The ability to obtain reliable VEMPs would most certainly be significantly improved by incorporating one of the commercially available video feedback systems that promote the maintenance of ongoing tonic contraction of the SCM.

In summary, we feel that we were able to obtain reliable and accurate results both with respect to peripheral vestibular and balance function in our study population. Addressing these issues of reliability and compliance was imperative before moving on to the discussion of the significance of the results obtained that follows in the subsequent sections beginning with our first experimental question.
4.2 What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?

4.2.1 Horizontal canal function

4.2.1.1 Caloric stimulation of horizontal canal function

Our results indicate an overall incidence of horizontal canal dysfunction of 53% (17/32) using a caloric stimulus. This overall incidence falls within the reported range of 23 to 76% for the larger comparable studies in adults (Huygen, Hinderink et al. 1995; Kiyomizu, Tono et al. 2000; Vibert, Hausler et al. 2001; Fina, Skinner et al. 2003; Buchman, Joy et al. 2004). This incidence is lower than that of a previous pediatric cohort, where preoperative dysfunction was found to occur in nearly 70% of cases (Buchman, Joy et al. 2004). Based on this figure, Buchman suggests that only a third of pediatric patients would be at risk of sustaining a vestibular injury due to cochlear implantation. However, our results demonstrate that only 28% of our study population demonstrated complete horizontal canal dysfunction bilaterally (9/32), 0.03% complete unilateral dysfunction (1/32) while the remainder (7/17) reflected mild (n=6) to moderate (n=1) unilateral hypofunction of the horizontal canal. If we interpret these results in same context as in Buchman’s study, the proportions are reversed, with approximately 30% of children demonstrating complete horizontal canal dysfunction and 70% having normal of sufficient horizontal canal function to be at risk of a vestibular injury due to cochlear implantation. A number of explanations could account for the differences in these two studies. The most important difference may be reflected in the etiology distribution between the 2 groups. As we will discuss in subsequent sections, the etiology of the SNHL is an important predictor of peripheral vestibular function. The Buchman study does not provide the etiologic breakdown specifically for the pediatric cohort however if significant differences existed between the two study populations this would explain in part the differences in the incidence of horizontal canal function. In the above section we have outlined the challenges of pediatric testing and certainly caloric irrigation is probably one of the most difficult tests in this population particularly when needing to identify complete dysfunction of the horizontal canal using a strong caloric stimulus (i.e. ice water). Although they do not specifically discuss patient compliance in their pediatric cohort, they do mention that all children with normal horizontal
canal function using caloric irrigation were over the age of 5 years of age at the time of testing. This raises two questions: 1) did compliance issues in the children under 5 years of age, lead to an overestimate of horizontal canal dysfunction? 2) Is there a difference in the incidence of vestibular dysfunction in children who are congenitally deaf compared to those who either have progressive or acquired deafness after the age of 5? These questions remain unanswered in Buchman et. al’s study however we feel strongly that our incidence of horizontal canal dysfunction is accurate for our study population given that complete dysfunction was verified with ice water irrigation in all cases. The issue of differences in the incidence of horizontal canal dysfunction in either progressive hearing loss or acquired hearing loss will be addressed in a subsequent section (4.3.2).

As previously discussed, in addition to a caloric stimulus, horizontal canal function can also be assessed by examining the VOR in response to rotation and this will be discussed further in the following section.

4.2.1.2 Rotational stimulation of horizontal canal function

Although the horizontal canal is viewed to be the ‘best tested’ of the vestibular end organs, typically only the lowest frequency range of horizontal canal function is tested through the use of a caloric stimulus. Although rotational chair testing accesses higher frequency horizontal canal function, previous studies in both adults and children, with and without cochlear implants, have looked at maximal rotation frequencies of only 0.64 Hz (Pappas 1981; Cyr, Brookhouser et al. 1985; Black, Lilly et al. 1987; Brey, Facer et al. 1995; Vibert, Hausler et al. 2001; Buchman, Joy et al. 2004). This is still considered to be in the low frequency range of horizontal canal function (Hess, Baloh et al. 1985; Shephard and Telian 1996; Hamid 2000). Several clinical tests including the high frequency head thrust test and dynamic visual acuity testing allow access to higher frequency horizontal canal function through head rotation at frequencies greater than 2Hz. It is however useful to supplement these clinical tests with other objective measures of horizontal canal function given that the subjective interpretation of the Halmagyi can be inaccurate (Kessler, Zarandy et al. 2007) and tests of dynamic visual acuity will only be abnormal in the setting of complete bilateral dysfunction of the horizontal semicircular canals. The use of objective eye movement recordings have certainly increased the
accuracy of high frequency head impulse testing, however, this has the added requirement of using a scleral coil technique or accelerometer and, to date, there is only one study that has used this technique in implanted adult patients (Migliaccio, Della Santina et al. 2005). A large proportion of rotary chairs are typically unable, because of mechanical limitations, to produce the torque required for high frequency rotation and high velocity step testing. These limitations are reflected in the literature where only relatively low frequencies of rotation (< 0.64 Hz) could be achieved when testing was conducted by this means (Pappas 1981; Cyr, Brookhouser et al. 1985; Black, Lilly et al. 1987; Brey, Facer et al. 1995; Vibert, Hausler et al. 2001; Buchman, Joy et al. 2004). The hydraulic nature of our custom built rotational chair (Zonich Technical Laboratories, Cincinnati Ohio) allows us to test frequencies up to 15 Hz. For the current study, a frequency range limited to 0.25 to 5.0 Hz was tested, given that beyond this range electrode slippage is a concern and thus the use of a scleral coil is required. Scleral coils have been used in children and infants (Weiss and Phillips 2006; Phillips 2007) however because of the difficulty and risk of corneal abrasion involved with inserting a contact lens into a moving child or infant we have limited our current use of scleral coils to older children. In addition scleral coils are tracked using an alternating magnetic field and therefore leads to a safety question with respect to the cochlear implant and the potential for inducing a current within the internal device. These systems have been used in patients with cochlear implants (Migliaccio, Della Santina et al. 2005) without reported ill effects and we hope to be able to do so in the future following additional safety studies. There are a number of reasons why employing high frequency stimuli is important in the assessment of both the normal and abnormal vestibular system. First, gaze stabilization at low frequencies of movement is dominated by smooth pursuit mechanisms and not the VOR. As the frequency of rotation increases the VOR begins to predominate and becomes the primary mechanism for gaze stabilization at high frequency (Grossman, Leigh et al. 1988). This may be particularly important consideration in the pediatric population where although the maturation of the VOR occurs early in post-natal life (Eviatar and Eviatar 1979; Ornitz 1983; Cyr, Brookhouser et al. 1985; Staller, Goin et al. 1986; Peterka, Black et al. 1987; Horak, Shumway-Cook et al. 1988), maturation of the neural mechanism underlying smooth pursuit occurs over a significantly longer time course and may not reach full maturity until the teen years (Herman, Maulucci et al. 1982). Secondly, in the setting of a vestibular lesion, compensation may occur and the VOR may recover at low frequencies of
function. However animal studies, where unilateral horizontal canal plugging was performed demonstrate that asymmetry of the VOR may persist but only become apparent at high frequency (Broussard, Bhatia et al. 1999). Therefore, failure to examine the VOR at high-frequency may lead us to inappropriately label the VOR and thus horizontal canal function, as normal or well-compensated.

In the current study, horizontal canal function as defined by a reduction in VOR gain during rotational chair testing occurred in 39% (14/36) of study subjects; 4 children with isolated high frequency losses were identified by this means. Although some asymmetries did exist, the majority of losses were bilateral in nature (13/14) with only a single child demonstrating a unilateral loss. The literature suggests an incidence of roughly 14% for unilateral deficits and 28%-30% for bilateral deficits using a low frequency rotation stimulus (<0.2 Hz) (Chiong, Nedzelski et al. 1994; Vibert, Hausler et al. 2001; Buchman, Joy et al. 2004). In 36 children with SNHL who either had received or were candidates for CI, the incidence of VOR abnormalities was 22% using passive low frequency (<0.05 Hz) rotation with ENG (Suarez, Angeli et al. 2007). We must however interpret these results in light of a number of substantial differences including dissimilarities in: 1) the study population, adults versus children, 2) the etiology of deafness across groups, and 3) the range of frequencies assessed, 0.25 – 5Hz in the current study versus at most 0.64 Hz for previous studies. The most relevant comparison for the incidence of abnormalities of the VOR is to the study by Migliaccio et al. where high frequency head thrusts were measured in 16 cochlear implant candidates using a scleral coil technique. They found that 36% of subjects demonstrated low VOR gains in one or both horizontal canals (Migliaccio, Della Santina et al. 2005). This incidence of VOR dysfunction is similar to that reported here although there remain important differences between the two study populations (adults vs. children), as well as differences in the underlying etiology of deafness.

In summary, using high frequency rotational chair testing not only allows us access to a spectrum of higher frequency function, it may also allow us to distinguish those with losses that lead to functional difficulties with balance versus those that do not. Also, we understand that isolated high frequency losses occur and can be symptomatic, carrying with them functional consequences for balance (Prepageran, Kisilevsky et al. 2005). These abnormalities can be
missed when we assess horizontal canal function using calorics or low frequency rotational testing alone and in the current study 4 individuals were identified with a purely high frequency loss of horizontal canal function.

Following this discussion of horizontal canal function, in the subsequent section we will discuss the incidence and relevance of saccular dysfunction in this same population.

4.2.2 Saccular function

A significant proportion of our study population (38%) demonstrated saccular dysfunction based on the absence of a VEMP response either bilaterally or unilaterally. These findings are consistent with a smaller study by Jin et al. who reported that 6/12 children with profound SNHL had abnormalities of saccular function and VEMP responses pre-operatively (Jin, Nakamura et al. 2006). The saccule is the vestibular end-organ that is most closely associated with the cochlea. During early development the otic vesicle divides into several chambers including a utricular chamber, which gives rise to the utricle and the semicircular canals, and a saccular chamber with gives rise to the saccule and the cochlea (O'Rahilly 1963). In some nonmammalian species, the saccule functions as a hearing organ (Furukawa and Ishii 1967). The original function of the inner ear is presumed to be a vestibular proprioceptor. Throughout evolution it is felt that transformations have occurred allowing for the detection of sound. Based on this notion of specialization, the inner ear is often viewed to consist of two separate divisions. The superior division consisting of the three semicircular canals and the utricle and the inferior division which included the saccule and the cochlea (Lowenstein 1936). Given the anatomic compartmentalization of the saccule and the cochlea one might predict that saccular function may be more likely to be affected than utricular or semicircular canal function in the presence of an inner ear injury leading to SNHL. While saccular dysfunction is seen in a large proportion of patients with SNHL, this prediction is not necessarily supported by our current findings or those in the literature with reported rates of saccular and horizontal canal function being relatively similar. Likely larger groups of subjects grouped according to etiology of SNHL would be required to definitively answer this question.
Although peripheral vestibular function is an important consideration in evaluating children with SNHL, what is likely more important clinically is their ability to maintain balance to a sufficient degree to carry out their activities of daily living. As such, in the following section we will specifically address balance performance in this group.

4.2.3 Static and dynamic balance function

Identifying a peripheral vestibular loss based on measures of functional balance in a child can be difficult. Depending on the specific functional test chosen, children with peripheral dysfunction can appear quite normal and this is evidenced by the fact that measures of bilateral coordination, strength, or running speed are not affected by loss of peripheral vestibular functional whether complete or partial, symmetrical or asymmetrical (Horak, Shumway-Cook et al. 1988). In addition, other more objective measures of motor coordination such as automatic muscle activation latencies, burst durations and sequencing in response to postural perturbation are likewise unaffected by vestibular sensitivity (Shumway-Cook and Horak 1986). Measures of postural alignment, muscle tone, prone extension, supine flexion and motor skills such as rapid forearm rotation, skipping and hopping also could not differentiate children with isolated vestibular losses from normal children (Fisher, Mixon et al. 1986). Therefore, identifying balance dysfunction can be difficult in children with SNHL. However, the results of the present work indicate that when children with SNHL are challenged by sufficiently difficult balance tasks that appropriately emphasize the contribution of the peripheral vestibular system, deficiencies in function surface. The variety of tasks that make up the balance subset of the BOT-2 provide this necessary gradation in level of difficulty and place emphasis on peripheral vestibular function. It is therefore deemed to be an appropriate tool that will adequately uncover functional deficits in children with SNHL over a wide range of ages (4 – 22 years) (Horak, Shumway-Cook et al. 1988). Even the subjective difference in performance between a subset of the children with SNHL in comparison to that of normal hearing children was readily apparent to those observing the administration of the BOT-2. Certainly as a group, the balance ability, based on BOT-2 performance, of children with SNHL is poorer than the standardized norms
although the range of abilities within this group spans a large spectrum. More importantly on an individual level, use of the BOT-2 has allowed us to accurately identify which children with profound SNHL have concurrent abnormalities of balance. There are a number of reasons we may suspect that children with SNHL may have poorer dynamic and static balance abilities. First this dysfunction may relate to underlying abnormalities in function of the vestibular end organs and we will address the correlation between balance performance using the BOT-2 and horizontal canal and saccular function in a later section (4.4). Secondly, even though the children in this study may have received auditory cues via their unilateral implants, given the absence of a bilateral auditory system, they would not have benefited from any of the directional cues or spatial information that may have been available to aid in maintaining balance. Although some children with deafness performed at or above the normative mean on the BOT-2, the performance of 70% falls below it. It is only those with the poorest scores that demonstrate concurrent deficits on vestibular end organ testing. Could the poorer performance of children with profound SNHL without an identifiable injury of the vestibular end organs be attributed to this lack or poor quality spatial cues that occur in the setting of deafness and exist even after rehabilitation with a unilateral implant? While we are quick to recognize the importance of visual, somatosensory and vestibular cues in the maintenance of balance, the contribution of hearing is rarely underlined and may be at play in explaining the overall poor balance performance seen in this study. Finally, other brain systems (i.e. motor cortex, cerebellum etc.) may have also been affected by the injury, lesion or mutation that led to the SNHL and these in turn may impact balance ability.

The auditory and vestibular end-organs share anatomic and phylogenetic similarities. Their membranous structure is continuous in nature and their receptor cells are similar in structure and organization. As a result, insults or injury to the inner ear that leads to SNHL may also disrupt peripheral vestibular dysfunction. Given the diverse types of injuries associated with the various etiologies responsible for SNHL, one might assume that the likelihood of vestibular dysfunction will be highly correlated to the specific inner ear injury. With this in mind, an extended discussion relating the potential and likelihood of an inner ear injury that leads to SNHL to also cause vestibular dysfunction will follow in the next section.
4.3 What influence does etiology and time course have on the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?

4.3.1 Etiology

In the following section we will discuss the specific incidence and pattern of peripheral vestibular and balance (dys)function that occurs in specific etiologies of deafness including meningitis, cochleovestibular anomalies, GJB2 deafness and SNHL of unknown etiology.

4.3.1.1 Meningitis

It is estimated that 5 to 35% of patients who survive meningitis experience partial to profound SNHL (Nadol 1978; Keane, Potsic et al. 1979; Berlow, Caldarelli et al. 1980; Dodge, Davis et al. 1984; Baldwin, Sweitzer et al. 1985). Although not as well studied the incidence of vestibular loss appears to be lower than that of SNHL and in the range of 3 to 12% (Lindberg, Rosenhall et al. 1977; Kaplan, Goddard et al. 1981). It is well known that bacterial meningitis can lead to precipitous ossification of the inner ear. However, the pathophysiology of the hearing and/or vestibular loss that can occur in the setting of bacterial meningitis however appears to relate more to an injury that occurs early on in the course of the disease. A number of studies have demonstrated that ataxia felt to be labyrinthine in origin can be either a presenting or early sign of bacterial meningitis (Bergstrand, Fahlen et al. 1957; Liebman, Lovrinic et al. 1969; Sproles, Azerrad et al. 1969; Schwartz 1972; Landthaler and Andrieu-Guitrancourt 1975; Roeser, Campbell et al. 1975; Lindberg, Rosenhall et al. 1977; Kaplan, Goddard et al. 1981). Although the details of the inner ear damage secondary to bacterial meningitis is not fully understood, spread of infection to the inner ear appears to occur primarily via the cochlear aqueduct and occasionally via the cochlear modiolus (Merchant and Gopen 1996). Histopathologic studies of temporal bones following meningitis have suggest that SNHL results from suppurative labyrinthitis which occurs in the acute phase of the disease (Merchant and Gopen 1996). Despite the inflammatory response seen in these specimens, the sensory neural elements of the auditory and vestibular systems were generally intact in these bones. A minority of specimens however demonstrated variable losses of the Organ of Corti and spiral ganglion cells and of the sensory cells of the cristae and maculae. Leukocytic infiltration of the
cochlear and vestibular nerves was also seen. Neurosensory structures also are generally intact in animal models even in cases with confirmed profound hearing loss (Bhatt, Halpin et al. 1991). This suggests perhaps that the SNHL or vestibular impairment resulting from meningitis results from biochemical alteration of the inner ear milieu or by ultrastructural changes not seen on light microscopy. With respect to the distribution of the inner ear injury, temporal bone studies suggest that the scala tympani was the most likely to be affected by this suppurative labyrinthitis with the most inflammation occurring in the basal turn. The scala vestibuli was affected in 50% of the temporal bones with the lateral semicircular canal being the most commonly involved site. Inflammation was not seen to involve the saccule or utricle in any cases (Merchant and Gopen 1996). The distribution of inflammation reported in these temporal bone studies parallels the pattern of ossification that we have seen in serial CT imaging in children with meningitis involved in the current study. This finding is also consistent with the fact that horizontal canal function was almost universally affected in our study population, whereas saccular function was well preserved in the majority of the children studied. The resistance of the saccule to injury in the face of a suppurative labyrinthitis that so dramatically affects the surrounding cochlea and semicircular canals is difficult to explain. If utricular function was likewise preserved in these children, this may support the theory that the more primitive otolithic organs are more resistant to injury from meningitis although it would still remain difficult to determine the pathophysiologic basis of this apparent resistance. In spite of the preservation of saccular function, static and dynamic balance function as measured by the BOT-2 was poorest in those children with acquired hearing loss due to meningitis.

4.3.1.2 Abnormal cochleovestibular anatomy

Static and dynamic balance ability in children with malformations of the cochlea and or vestibular apparatus were poor and only marginally better than those of children with acquired hearing loss. Balance dysfunction was accompanied by loss of horizontal canal function in a large proportion of these children, 67% to 75% based on caloric and rotational stimuli respectively. The reason for this high degree of association is found on CT imaging of the temporal bone. In the current study, of the 5 children with temporal bone anomalies, 3 (60%) demonstrated abnormalities of the vestibule and semicircular canal ranging from mild dysplasia to complete agenesis (Figure 3.8). Only a single child demonstrated abnormal horizontal canal
function without an apparent abnormality of the semicircular canals on CT imaging. Based on this finding, in the majority of cases vestibular dysfunction in the setting of cochleovestibular anomalies can be attributed to gross abnormalities in the formation of the vestibular end-organs. Another possibility which would also explain the case of vestibular dysfunction in the setting of a normal appearing vestibular apparatus, is that malformation of the cochlea and or vestibular end-organs are only an indicator of ultrastructural abnormalities within the inner ear and are not themselves directly responsible for the dysfunction.

4.3.1.3 GJB2 related deafness

It is known that GJB2 mutations lead to mutations in the connexin 26 gene causing altered gap junction coupling in the inner ear. The SNHL is believed to result from altered potassium homeostasis which leads to an impairment of the endocochlear potential (Forge, Becker et al. 2003). Similar to the cochlea it has been shown that the vestibular receptors of the otolithic organs and the semicircular canals are also coupled by gap junction networks (Kikuchi, Adams et al. 1994). This network is responsible for creating a depolarization-dependent increase of potassium around the vestibular hair cell synapses (Furukawa 1985) as is the case for the outer hair cells of the cochlea (Johnstone, Patuzzi et al. 1989). Based on these similarities one might predict that vestibular end organ function may be affected by mutations in the GJB2 gene. However, in comparison to children with hearing loss due to meningitis or cochleovestibular anomalies, the performance of children with SNHL related to mutations of the GJB2 gene was visibly better. There was, however, much more variability within this group and performance spanned the spectrum from above average to well-below average. The incidence of vestibular end organ dysfunction in GJB2 related deafness also lower. The majority of children with SNHL due to GJB2 had relatively normal horizontal canal function with a small number demonstrating mild unilateral dysfunction, all of which occurred on the implanted side. All children had normal horizontal canal function indicated by a normal VOR to rotation, highlighting mild and compensated nature of these losses. Saccular function was absent bilaterally in a minority of children with GJB2 related deafness (1/9) and several demonstrated absence on only the implanted side (4/9).
Two children with GJB2 deafness however demonstrated very different results, having complete horizontal canal dysfunction on caloric and rotational chair testing. These phenotypic differences may reflected by differences in the GJB2 mutations expressed in these children. Both children with complete horizontal canal dysfunction demonstrated similar mutations of the GJB2 gene (i.e. E114G/I203T/V27I and V27I/I203T). It is unclear at this time whether these GJB2 mutations are disease causing or simply polymorphisms and further study is required to further clarify the significance of these mutations with respect to vestibular function.

Overall, to date there are limited reports of vestibular function in the setting of GJB2 related deafness to which to compare our results. The largest report in the literature includes 7 patients with variable degrees of sensorineural hearing and different mutations in GJB2. In this study, horizontal canal function was normal in all but one patient, saccular function was absent in the majority (5/7). While our results for horizontal canal function are similar with the exception of our 2 patients with complete dysfunction, saccular function was preserved in the majority of our patients in contrast to Todt’s study (Todt, Hennies et al. 2005). Absence of saccular function in the setting of GJB2 related deafness has also been demonstrated in two other single patient reports (Tsuzuku, Kaga et al. 1992; Jun, McGuirt et al. 2000). This difference in results may reflect differences in characteristics of the patient populations examined with respect to degree of hearing loss, type of GJB2 mutations and heterozygosity or homozygosity of these mutations. While we tend to lump together all subjects with GJB2 related deafness, already over 100 mutations have been described in the GJB2 gene (Ballana, Ventayol et al. 2007) and certainly support for phenotypic differences exists (Cohn, Kelley et al. 1999; Snoeckx, Huygen et al. 2005).

While many similarities in the makeup of the sensory epithelium and surrounding fluid compartments, specific differences in the morphophysiology of the cochlea and the vestibular end-organs do exist. For example, in contrast to auditory afferents, the afferents of the vestibular end organs are subject to resting discharge (Lowenstein and Sand 1936). Presumably the variable impact of some GJB2 mutations on cochlear and vestibular end organ function relates to differences for example at the level of the efferent inputs, composition and response properties of ionic channels between these two systems. However specific discussion regarding differences in ionic channels and their individual kinetics which may be responsible for the
presence or absence of vestibular dysfunction in the setting of GJB2 related deafness is beyond the scope of the current thesis.

4.3.1.4 Unknown etiology

Balance ability in the setting of SNHL of unknown etiology was on average relatively normal, however individual performance did again span a large spectrum with some children demonstrating very poor abilities. In this group, 42% of the children with hearing loss of unknown etiology, demonstrated horizontal canal dysfunction based on caloric testing. The degree of dysfunction ranged from mild unilateral losses in the implanted ear to bilateral areflexia. Twenty-six percent demonstrated dysfunction of the horizontal canal based on an abnormal VOR on rotational chair testing. Given the likely heterogeneity of the underlying causes of SNHL in this group it becomes difficult to discuss the association between SNHL and vestibular end-organ and balance dysfunction. This highlights the importance of thoroughly investigating the etiology of the SNHL as well as continuing to identify additional genetic causes of deafness which likely comprise the majority of the currently unknown etiologies within this group. On the flip side, identifying dysfunction of the vestibular end-organs in a child with SNHL can also help direct the search for an underlying genetic cause known to be associated with severe vestibular dysfunction such as Usher’s syndrome type I.

While many different etiologies of SNHL exist, likewise the time course of the SNHL is also variable and can range from congenital to acquired, sudden versus progressive. Certainly such differences may also reflect differences in the time course of an accompanying vestibular loss and this will be considered in the following section.

4.3.2 Time course of hearing loss: progressive versus non-progressive

Differences in balance ability as estimated by BOT-2 performance were both observed and demonstrated statistically when comparing the results of children with progressive versus non-progressive SNHL. Although the number of children with progressive losses were few in the current study (n=4), as a group they did demonstrate better performance on the BOT-2 irrespective of horizontal canal function. Just as children with progressive auditory losses are able to develop speech and language given an adequate minimum access to sound, presumably there may be a parallel mechanism which occurs within the vestibular system in relation to
developing adequate balance in the presence of a progressive vestibular loss. Presumably, a slow progressive loss of vestibular function, would allow access to at least weak vestibular signals over a period of time and that may be sufficient enough to generate appropriate motor responses. Depending on the time course of the loss of function, perhaps even a gradual substitution or shift of the importance of other sensory inputs (visual, proprioceptive and possibly even vestibuulospinal) in the maintenance of balance may have occurred.

Now that we have discussed the incidence of vestibular end organ and balance function in the setting of SNHL, we will move on to discuss the correlation between tests of peripheral vestibular and balance function in the following section.

4.4 Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?

Of the tests of vestibular end organ function employed in the current study, performance on high frequency rotational chair testing displayed the strongest and most robust correlation with static and dynamic balance ability as measured by the BOT-2 in our subject population. Horizontal canal dysfunction based on caloric areflexia was also correlated with balance ability; however, horizontal canal function based on rotational chair testing also identified an additional population of children with isolated high frequency loss, which was deemed clinically significant based on their poor performance on the BOT-2. This population is easily missed by caloric testing alone. Other advantages to rotational chair testing is that it is presumably better tolerated than caloric testing, particularly given that confirmation of bilateral areflexia requires the use of ice water caloric irrigation. In summary, our results suggest that caloric testing may identify horizontal canal dysfunction that is not clinically significant likely as a result of physiologic compensation (see section 4.6 for further discussion) and may also miss clinically significant high frequency losses of function identified by rotational chair testing. For these reasons, we feel that the true incidence of vestibular dysfunction in our study population is likely best predicted by abnormalities of the VOR response to high frequency rotation.

When examining vestibular function in children with SNHL and unilateral cochlear we need not only consider the baseline incidence of peripheral vestibular function but also the
implications that surgical implantation itself may have on function. This consideration will be discussed thoroughly in the following section.

4.5 Does cochlear implantation alter vestibular end organ function?

Histopathologic analysis of temporal bones and the vestibular apparatus following cochlear implantation have demonstrated injury in more than half of patients. As previously mentioned (section 1.8), histologic abnormalities following implantation have included fibrosis of the vestibular apparatus, saccular membrane distortion, osteoneogenesis and reactive neuromas. In addition involvement of the scala vestibuli, as a result of damage to the osseous spiral lamina or basilar membrane in the cochlear basal turn, correlated strongly with vestibular end-organ damage (Tien and Linthicum 2002).

Adults undergoing cochlear implantation more often experience transient vestibular systems post-operatively in comparison to their pediatric counterparts. In our program, approximately 1.2% of children (7/575) have experienced transient symptoms of vestibular dysfunction with the only identifiable risk factors being, symptomatic episodic vertigo prior to implantation and in the case of re-implantation, dizziness at the time of their first surgery as well as reimplantation itself. This is significantly lower than the incidence estimates of 2 to 49% of adults who experience symptomatic vertigo following implantation found in the literature (Black, Lilly et al. 1987; Cohen, Hoffman et al. 1988; Webb, Lehnhardt et al. 1991; Huygen, van den Broek et al. 1994; Ito 1998; Kempf, Johann et al. 1999; Ribari, Kustel et al. 1999; Kubo, Yamamoto et al. 2001; Enticott, Tari et al. 2006).

The current subject population allows for a limited evaluation of the impact of cochlear implantation on balance and vestibular end organ function given that at the time of testing they already had a unilateral implant. In our study population we can examine the difference in VOR gain in response to a rotational stimulus on the implanted versus non-implanted side. In our analysis, no significant asymmetry was found suggesting little effect of implantation on VOR gain measured by rotational chair testing. In a similar analysis involving lower frequencies of rotation (0.01-0.32 Hz); Buchman et al. noted some changes in post-operative rotational chair testing at one year. These differences were small and not consistent across the multiple comparisons through the entire frequency range (Buchman, Joy et al. 2004). In this same study,
a significant reduction in caloric function occurred on the implanted side in 29% (8/28) with deterioration defined as a reduction of \( \geq 21^\circ/\text{sec} \) in the summed warm and cool responses for a given ear which persisted at the 1 to 2 year interval following surgery (Buchman, Joy et al. 2004). In the current study, of those children with mild to moderate unilateral hypofunction, all but one (83%) occurred on the side of implantation. The fact that a large number of these excitability differences were mild in nature raised the possibility that a post-surgical change in the thermal stimulability of the lateral canal could have occurred and may be an alternative explanation. No studies to date have specifically examined changes in thermal stimulability resulting from the mastoidectomy with a facial recess approach necessary for implantation, however, it has been demonstrated that temperature dissipation in the middle ear during caloric irrigation changes according to the degree of aeration in the temporal bone (Zangemeister and Bock 1979; Proctor 1982; Pau, Sievert et al. 2001). This theory is further supported by the fact that when we exclude those children with mild horizontal canal hypofunction ipsilateral to their implant, our overall incidence of caloric dysfunction decreases to 32% which is much more consistent the incidence of VOR abnormalities detected on rotational chair testing (39%).

Compared to the horizontal semicircular canal, the saccule may be more susceptible to damage than the utricle or semicircular canals because of its proximity to the insertion path of the implant’s electrode array (Tien and Linthicum 2002). In the current study there was a trend that unilateral saccular dysfunction occurred more commonly on the implanted side.

The majority of the children participating in our study demonstrated sufficient peripheral vestibular function to be considered at risk of sustaining an injury due to implantation. However surgical injury was not a consideration for just over 1/3 of patients who demonstrated minimal to absent function of the horizontal canal and saccule. Despite the severity of the vestibular in this group, all children ambulated without difficulty and many of those with the most profound losses were involved and succeeding in many activities that challenge balance. The function of these children despite severe losses of vestibular function is a reflection of compensation secondary to a reliance on other inputs (i.e. visual and somatosensory) that contribute to the maintenance of stability. A discussion of the strategies at play that allow these children to lead normal lives despite these severe losses continues in the following section.
4.6 Strategies for compensation after bilateral peripheral vestibular loss

The maintenance of balance and stability results from a complex interplay between the peripheral vestibular, visual and somatosensory system. Fortunately, considerable overlap in the handling of sensory information between these systems exists. This redundancy promotes and facilitates adequate function in the presence of perceptual and physical disturbances, as well as when the function of any one of these systems is lost, compromised or distorted. The current study sample lends itself to examining the compensatory strategies at play in the setting of congenital and early acquired vestibular loss. In our population, profound bilateral areflexia of the horizontal semicircular canals, was present at birth or acquired during early childhood, with only a single child being over the age of 5 years at the time of the acquired loss. The time course of an insult is important given that differences in the compensatory strategies employed likely exist and change over time. The relative importance and contribution of each of the sensory and motor systems that work together to maintain balance is not static but rather fluctuates according to the characteristics of the sensory information at any one point in time. Therefore, the question of how children with combined cochleovestibular loss compensate cannot be answered without understanding the characteristics of the sensory environment in which they find themselves. In the current study, we have demonstrated that the relative importance of vision on the maintenance of balance is unchanged in the presence of a bilateral vestibular loss. This was reflected in that all children, normal hearing, deaf, with and without concurrent vestibular dysfunction suffered a proportionally identical decrement in performance on certain items on the BOT-2 when the eyes were closed (Figure 3.7).

Attempts have been made to identify the compensatory strategies for maintaining postural control employed by subjects with congenital or early acquired bilateral vestibular loss. Theoretically, Mergner’s model of postural orientation suggests that when somatosensory and vestibular information interpret the surface as stable, one can rely on somatosensory information alone to control and maintain posture. However, the maintenance of postural control when a surface is interpreted as unstable, results from a decreased reliance on surface somatosensory information and an increased reliance on vestibular information (Mergner and Rosemeier 1998). More specifically, some studies have aimed to determine the relative weighting of different sensory receptor systems in the congenital or early acquired absence of peripheral vestibular...
input by examining postural control using posturography under a number of sensory conditions (Enbom, Magnusson et al. 1991). This study suggests that children with normal cochleovestibular function and those with bilateral vestibular loss are indistinguishable based on postural sway when only one sensory system is distorted, for example, standing with eyes open or closed on a solid surface or with eyes open on foam rubber. However, children with bilateral vestibular loss were easily distinguished from controls when two simultaneous sensory distortions are applied, such as when any two of the following are combined, eyes closed, calf vibration or foam surface. The degree to which these sensory perturbations disrupt postural control was however variable. For example, the increase in body sway elicited by eye closure was similar in the two groups, regardless of the presence of foam surface or calf vibration. Similarly, the application of muscle vibration while standing on a solid surface increased sway velocity to a similar degree in children with normal versus abnormal cochleovestibular function. However when either the eyes were closed and/or in the presence of muscle vibration, the simultaneous distortion of pressor reception caused by standing on foam rubber, led to a proportionally larger increase in sway in children with bilateral vestibular loss. This suggests that in the presence of bilateral vestibular dysfunction, the strategy for postural control is unevenly redistributed to the visual, proprioceptive and exteroceptive receptors with increasing importance placed on pressor reception and proprioception while the relative importance of vision on postural control remains unchanged. This is in keeping with the findings of the current study where in children with bilateral loss of horizontal canal function, the impact of vision was not overrepresented. This however is in contrast to the findings in a number of adult studies where in similar tasks, adults with acquired vestibular loss were found to depend much more heavily on visual cues and where eye closure resulted in proportionally worse postural instability compared to control subjects (Bles and de Jong 1986; Buchanan and Horak 2001). It has been suggested also that the ability to control the head independent of the trunk is important for postural compensation following vestibular loss. Individuals who suffer vestibular loss in infancy retain their ability to separate head and trunk motion and thus control their head in a manner more similar to age-matched controls than do adults with later onset vestibular loss and thus have better overall performance on tasks testing static and dynamic balance (Shupert and Horak 1996; Buchanan and Horak 2001). Others studies in children have corroborated the relative importation of somatosensory information in the setting of a bilateral vestibular loss.
These studies demonstrate near-normal postural sway in sensory conditions when either accurate surface or visual information are available while sway significantly increases when the surface is sway referenced suggesting again that compensation is highly dependent on pressor and proprioceptive inputs even when eyes are open (Black, Wall et al. 1983; Black and Nashner 1984; Shumway-Cook and Horak 1986; Horak 1987).

In summary, in the presence of bilateral vestibular dysfunction, the strategy for postural control in children is likely unevenly redistributed to the visual, proprioceptive and exteroceptive receptors with increasing importance placed on pressor reception and proprioception while the relative importance of vision on postural control remains unchanged. As a consequence of the efficacy of the compensatory mechanisms for sensorimotor control tests of postural control must be adequately sensitive otherwise even bilateral vestibular areflexia may be missed by employing simple tests such as the Romberg. In addition, the visual and somatosensory conditions should be systematically and incrementally manipulated in order to partition the use of alternative interacting sensory components of postural control.

4.6.1 Time course to compensation

For those individuals with acquired vestibular loss, the duration of the loss is likely an important predictor of the degree of compensation. Buchanan and Horak point out that one of the main differences between the well and poorly compensated patients in their study, was the duration of vestibular loss; the loss extended for at least 2 years in the well compensated cohort, and less than 1 year in the majority of the poorly compensated subjects (Buchanan and Horak 2001). Degree of dysfunction at the level of the vestibular end organs may help to explain the slower time course or inability to compensate in some individuals even after prolonged interval since the loss of function. In this same study, one patient who was 2 years post-lesion and poorly compensated for vestibular loss, demonstrated normal dynamic and static otolithic function whereas the compensated counterparts who had lesions of similar duration and absence of otolithic function. Perhaps a sensory deficit associated with a complete loss of vestibular end organ function is more quickly and easily overcome than a deficit associated with a partial loss.
that produces an incomplete reference leading to confounding sensory information (Buchanan and Horak 2001).

Just as the primary strategy employed to compensate for a vestibular loss likely changes depending on the sensory context, this strategy may also change over time. As an example, a longitudinal study of patients with acquired labyrinthine dysfunction tested using a tilting room paradigm suggested that the relative emphasis on visual and somatosensory information shifted over time. Specifically, in early recovery, primary dependence was on visual information while in the long term the relative weight given to somatosensory information increased (Bles, de Jong et al. 1984). Despite the very best compensation after an acquired vestibular loss, there are limits and compensation is likely to breakdown under particularly challenging situations. In this same study, learned improvements in postural stability occurred over time with repeated exposure to the tilting room, however these improvements were limited to relatively low frequencies of motion (< 0.2 Hz) while no improvements or compensation were seen over time at frequencies > 0.2 Hz (Bles, de Jong et al. 1984). This reemphasizes the increasing reliance on vestibular end organ function in the setting of an unstable surface (Mergner and Rosemeier 1998). This breakdown in compensation was also observed in the current study when children with bilateral vestibular losses were asked to perform challenging balance tasks where either vision or stability was altered. Although likely, further study would be required to determine whether or not similar limitations to compensation exist at high frequency in the pediatric setting.

4.7 Deficits of Sensory Integration

Up until this point we have focused on the functional consequences of vestibular end organ dysfunction, and more specifically, dysfunction of the horizontal canal. However maintenance of balance and co-ordination results from a complex interplay between the peripheral vestibular system, central sensory and motor systems. Therefore, any abnormality which interferes with the integration between these systems would also impact balance and co-ordination. With this in mind, a child with abnormalities at the level of sensory integration may have a normal VOR and caloric function while demonstrating an inability to maintain posture in situations of sensory conflict. Three such children were featured in a study by Crowe and Horak
and demonstrated impairments of sensory organization which led to poor performance on all motor proficiency measures as opposed to only those that stress the contributions of vestibular input. The lesion may lie in the coordination of sensory inputs and it is also possible that these children have underlying vestibular end organ dysfunction that cannot be measured by the currently available tests. For example, a peripheral lesion within the vertical canals or the otolithic organs, or a deficit of horizontal canal function at a frequency above that evaluated by the rotational stimulus (0.2 and 0.05 Hz) may be present but undetected (Crowe and Horak 1988). Several children in our study had surprisingly poor static and dynamic balance based on BOT-2 scores despite normal tests of vestibular end organ function. The performance of these children may reflect a deficit of sensory integration. In contrast, one child who had particularly low age adjusted scores on all items of the BOT-2 had normal caloric function but a demonstrable loss of high frequency function on rotational chair testing (> 1 Hz) which was undetected by caloric stimulation and would have been missed with low frequency rotational testing alone. Labeling study subjects as having either normal or abnormal vestibular end organ function based solely on tests of horizontal canal function, is an oversimplification especially when only a restricted frequency range is tested. It has been demonstrated that low frequency canal function can be normal in the presence of a high frequency loss (Prepageran, Kisilevsky et al. 2005) and that vertical canal function can be abnormal independent of horizontal canal function (Migliaccio, Della Santina et al. 2005). The central connections of the vertical canals and otoliths, whose primary functions include stance and posture control, and those of the horizontal canals which drive the VOR are different. It is therefore possible that localized brainstem abnormalities could result in different functional effects on the two systems and that independent lesions could affect either the ascending vestibulo-ocular or descending vestibulo-spinal pathways (Schwindt 1981; Wilson 1981; Ornitz 1983).

4.8 Clinical Relevance

Clinical examination is certainly the first line in evaluating any child with potential SNHL or vestibular dysfunction. The current study suggests that from the point of view of clinical examination, the high frequency head thrust test and a test of dynamic visual acuity (DVA) as well as an objective assessment of static and dynamic balance such as the BOT-2 would be the highest yield in identifying children with vestibular and balance dysfunction. We
would expect oscillosia on DVA in those children with bilateral vestibular losses, due to an inability to use their VOR to stabilize the retinal image during rapid self-motion. Abnormalities of the high frequency head thrust test would occur in children with significant unilateral or bilateral losses resulting in an inability of their VOR to generate accurate production of equal, but opposite conjugate movements of the eyes relative to the head. In the current study, some children with significant losses demonstrated subjectively normal clinical tests in cases where the vestibular dysfunction would have predicted them to be abnormal. This finding is echoed in previous studies demonstrating that the correlation between the clinical detection of an abnormal Halmagyi and that performed with a scleral coil was only intermediate and that clinical Halmagyi may lack specificity (Kessler, Zarandy et al. 2007). Therefore although clinical examination is a very important part of evaluating the child with SNHL, significant vestibular disturbance can be missed and therefore coupling the clinical exam with adjunctive tests or adding to it an objective component (i.e. head thrust with DC-ENG or sclera coil monitoring) may dramatically increase the yield and accuracy of the diagnosis.

What is the clinical importance of identifying children with vestibular dysfunction? Over the last decade increasing emphasis has been placed on the need for the early identification of children with hearing impairment with the target of having such children aided by 6 months of age, a goal which is now routinely achieved. In the setting of hearing rehabilitation, there is a clear relationship between early intervention and outcome. Although difficult to estimate because of the impact of etiology and residual thresholds, for all-comers with SNHL the incidence of a simultaneous vestibular lesion is likely around 30%. Despite this correlation we have not taken the same aggressive approach to identifying and rehabilitating the concurrent vestibular impairment. There are a number of reasons why we should strive to do so. First, identifying peripheral vestibular dysfunction prevents the false labeling of children as having global delay, central lesions or multiple handicaps. Secondly, different therapeutic approaches can be used for the rehabilitation of children with either loss of vestibular sensitivity or deficits of sensory organization. For example, children with SNHL and reduced or absent vestibular dysfunction, may benefit from balance strategies in various environmental contexts in an effort to prime their visual and somatic senses facilitating compensation. Children with sensory organization deficits would benefit from a more global intervention program designed to address
problems such as deficits in bilateral coordination and inability to resolve sensory conflict situations. More specifically, interventions as simple as a 10 day exercise program focused on activities of static balance activities led to significant improvement in standing balance duration in children with SNHL compared to untreated hearing impaired controls (Effgen 1981).

At a minimum, bilateral vestibular loss carries with it a number of clinical safety concerns that should certainly be relayed to patients. These include the potential for loss of spatial orientation when swimming under water as well as in the dark and reports of drowning have occurred in patients where loss of bilateral loss of vestibular function was likely (Verhagen, Huygen et al. 1987). Although such limitations are obvious to clinicians, they often are not to patients and their parents. Given the reliance on proprioception to maintain balance, children with vestibular dysfunction should also be counseled about the importance of maintaining a healthy lifestyle and adapt preventive measures avoiding and aggressively treating illnesses such as diabetes which are known to induce loss of peripheral proprioception.

Even in the advent of universal neonatal hearing screening some children with profound SNHL remain unidentified for a number of reasons. Understanding the correlation between vestibular function and hearing impairment is important in this setting given that vestibular dysfunction may lead to delays in reaching motor milestones which may provide an indication of either a progressive or missed hearing loss. Proper assessment of a gross motor delay (sitting, walking) in the absence of deficits in fine motor function could lead to earlier identification than would occur with the failure to develop language, the true hallmark of hearing loss.

Excellent, although incomplete compensation appears to occur in many children with bilateral vestibular deficits, therefore eliciting abnormalities on functional testing may be quite difficult. Also, given the absence of normal vestibular input since infancy, these individuals and/or their parents may not recognize the child’s difficulties when riding a bicycle, walking on a balance beam or orienting themselves in the dark. In order to be sensitive indicators of peripheral vestibular loss, tests of balance must place individuals in an environment without redundant visual and surface sensory inputs or require movement patterns in which vestibular input is critical.
Finally, before we can even begin to understand and measure the implications, for better or worse, of unilateral and/or bilateral cochlear implantation on vestibular end organ and balance function, we need to be certain that our baseline measures are accurate and adequately reflect functional outcome. An understanding of baseline vestibular function may also allow us to experiment with the properties of cochlear implants in an effort to increase the quality of the sensory information provided to children with concurrent lesions of the cochlea and the labyrinth. As we are identifying an ever increasing number of genes responsible for SNHL, the vestibular phenotype of these children has already begun to narrow and dictate the search for the genetic etiology of their hearing loss (i.e. any child with bilateral areflexia is tested for the Usher’s syndrome gene) and will most certainly continue to do so in the future.

4.9 Future direction

The current study has prompted a line of questioning that could last for a career. In the short term, we aim to better clarify the impact of bilateral implantation on vestibular end organ and balance function, by repeating the caloric, rotational chair, VEMP and BOT-2 testing following sequential bilateral implantation. In addition a cohort of older children with primarily progressive losses are being investigated pre-operatively using the same techniques to further characterize the relationship between and elucidate the relationship between progressive SNHL and vestibular and balance function. As long term goals, we aim to follow these pediatric patients with vestibular disturbances over time to determine how compensation of their vestibular loss changes as visual acuity and proprioceptive sensitivity decrease with age and concurrent illness. In addition, we hope to learn more about the potential for optimizing balance through the use of hearing rehabilitation and cochlear implantation given that implantation may carry the potential to benefit vestibular end organ function and balance. We feel that this is a reasonable hypothesis based on several preliminary studies including one of our own where dynamic balance performance of children was improved when wearing their unilateral implants activated in ambient noise (Cushing SL 2007). Similar findings have been shown in adults with CI, where poorer stability on posturography was seen when the implant was turned off, with small gains in stability occurring with the device on and activated in quiet and further improvements noted when the device was activated in the presence of a non-cuing noise source (Eisenberg, Nelson et al. 1982; Buchman, Joy et al. 2004). These improvements in
balance may be occurring either secondary to increased access to cuing and spatial information in sound or may be the result of the delivery of a low level of electrical stimulation via the implant to the vestibular end organs and primary afferents. Further study is most certainly required to elucidate these potential benefits of cochlear implantation to improvements in balance function and this may be particularly relevant to those children who demonstrate severe bilateral peripheral vestibular dysfunction.
CHAPTER 5: CONCLUSIONS

At the outset we aimed to better define the relationship between sensorineural hearing loss and vestibular end organ and balance function in children. This was done keeping in mind the caveat that we first needed to establish a reliable means of testing vestibular end organ function that also correlated well with functional balance. Although we would still favour a battery of overlapping tests, including caloric and VEMP testing, high frequency sinusoidal rotational appears to provide the most reliable means of assessing horizontal canal function across the entire frequency range of horizontal canal function. Likewise, we have shown that when measured in this fashion, horizontal canal function correlates well with static and dynamic balance ability. The final obstacle was to subdivide our study population into realistically homogeneous groups with respect to degree and etiology of the SNHL. This was achieved by studying only children with unilateral implants given that baseline hearing would have at a minimum been severe to profound bilaterally and using all available historical, clinical, radiologic and genetic information to appropriately classify subjects according to etiology. We estimate that clinically significant vestibular dysfunction as assessed by high frequency rotational chair testing occurs in approximately 39% of children who are candidates for cochlear implantation. When broken down with respect to etiology, nearly all children with SNHL due to meningitis have a parallel injury of the horizontal canals with preservation of saccular function. Similarly, cochleovestibular anomalies typically, although not always, portend cochleovestibular dysfunction. Horizontal canal dysfunction as estimated by abnormalities of the VOR during rotation was not demonstrated in the majority of children with GJB2 related deafness, with the exception of two children with a particular gene mutation (E114G/I203T/V27I). As expected the group of children whose hearing loss was classified as unknown had a more variable relationship between auditory and vestibular function, a reflection of the heterogeneity inherent to this group.

This dataset represents the first evaluation of low and high frequency horizontal canal and saccular function in children who are candidates for CI and its correlation to functional outcome, using a standardized method of assessing static and dynamic balance. More importantly it reminds us that acknowledgement of the high incidence of vestibular and balance
dysfunction that accompanies SNHL is essential in the care of the hearing impaired child. This is more important than ever given the success achieved in the rehabilitation of children with profound sensorineural hearing loss with cochlear implants.

Although more research is required, from a physiological perspective, involvement or absence of involvement of the vestibular end organs by cochlear pathology may lend insight into the specific characteristic of the insult leading to various etiologies of SNHL. This in turn could lead to the identification of potential therapeutic targets within the cochlea and vestibular end organs. As our population ages, hearing and balance will come to the forefront of both preventive and therapeutic medicine and the key to achieving adequate and appropriate compensation in the presence of a peripheral vestibular loss, may lie within the reach of the congenitally or early deafened child.
CHAPTER 6: REFERENCES


## APPENDIX 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>CI Side</th>
<th>Progressive SNHL</th>
<th>Etiology</th>
<th>VEMP</th>
<th>Caloric</th>
<th>Rotational Chair</th>
<th>BOT2 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R L</td>
<td>R L</td>
<td>All High Hz</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12.3</td>
<td>R</td>
<td>N</td>
<td>M</td>
<td>N N</td>
<td>N A A</td>
<td>A A 3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>9.9</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>N N</td>
<td>A A A</td>
<td>A A 3</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>10.2</td>
<td>R</td>
<td>N</td>
<td>Ab</td>
<td>N A</td>
<td>A A A</td>
<td>A A 6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>A N</td>
<td>A A A</td>
<td>A A 7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9.5</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>.</td>
<td>.</td>
<td>N N 7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8.2</td>
<td>L</td>
<td>N</td>
<td>M</td>
<td>N N</td>
<td>A A A</td>
<td>A A 7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7.5</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>N N</td>
<td>N N N</td>
<td>N N 8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15.6</td>
<td>R</td>
<td>N</td>
<td>M</td>
<td>.</td>
<td>.</td>
<td>N N 8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>12.1</td>
<td>R</td>
<td>N</td>
<td>M</td>
<td>N N</td>
<td>A A A</td>
<td>A A 9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12.1</td>
<td>R</td>
<td>N</td>
<td>Ab/C</td>
<td>N N</td>
<td>A A A</td>
<td>A A 9</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>19.3</td>
<td>R</td>
<td>N</td>
<td>Ab</td>
<td>.</td>
<td>.</td>
<td>N N 9</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4.6</td>
<td>R</td>
<td>N</td>
<td>M</td>
<td>N N</td>
<td>A A A</td>
<td>A A 9</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>9.3</td>
<td>R</td>
<td>N</td>
<td>M</td>
<td>A A</td>
<td>A A A</td>
<td>A A 10</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>5.4</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>N N</td>
<td>A M H</td>
<td>N N 10</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4.8</td>
<td>L</td>
<td>N</td>
<td>U</td>
<td>I I</td>
<td>N N A</td>
<td>A A 12</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>12.5</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>N N</td>
<td>A M H</td>
<td>N N 13</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4.8</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>I I</td>
<td>N N A</td>
<td>N N 13</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>17.8</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>A A</td>
<td>N N N</td>
<td>N N 13</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>17.9</td>
<td>R</td>
<td>N</td>
<td>Ab</td>
<td>.</td>
<td>.</td>
<td>A A 13</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>7.5</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>A A</td>
<td>N N N</td>
<td>N N 13</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>13.9</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>N N</td>
<td>N N N</td>
<td>N N 13</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>3.4</td>
<td>R</td>
<td>C</td>
<td>I I A</td>
<td>M H</td>
<td>N N A</td>
<td>N N 15</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>5.3</td>
<td>L</td>
<td>N</td>
<td>C</td>
<td>I I</td>
<td>N N A</td>
<td>N N 16</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>10.6</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>N N</td>
<td>A M H</td>
<td>N N 17</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>16.0</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>.</td>
<td>.</td>
<td>N N 17</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>5.6</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>N N</td>
<td>A M H</td>
<td>N N 19</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>15.7</td>
<td>R</td>
<td>Y</td>
<td>U</td>
<td>N N</td>
<td>A M H</td>
<td>N N 19</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>4.4</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>.</td>
<td>.</td>
<td>N N 20</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>17.3</td>
<td>R</td>
<td>Y</td>
<td>U</td>
<td>.</td>
<td>.</td>
<td>A A 22</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>13.7</td>
<td>R</td>
<td>Y</td>
<td>C</td>
<td>A A</td>
<td>N N N</td>
<td>N N 23</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>6.0</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>.</td>
<td>.</td>
<td>N N 24</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8.6</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>A A</td>
<td>N M H</td>
<td>N N N</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>6.8</td>
<td>L</td>
<td>N</td>
<td>M</td>
<td>A A</td>
<td>A A A</td>
<td>A A 8</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>5.6</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>N N</td>
<td>N N N</td>
<td>N N 8</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>4.2</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>A N</td>
<td>N N N</td>
<td>N N 15</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>4.6</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>N I</td>
<td>N N N</td>
<td>.</td>
<td>13</td>
</tr>
<tr>
<td>37</td>
<td>4.4</td>
<td>L</td>
<td>N</td>
<td>C</td>
<td>A N</td>
<td>N N N</td>
<td>.</td>
<td>22</td>
</tr>
<tr>
<td>38</td>
<td>10.9</td>
<td>R</td>
<td>Y</td>
<td>Ab</td>
<td>.</td>
<td>.</td>
<td>N N 10</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>6.3</td>
<td>R</td>
<td>N</td>
<td>C</td>
<td>N I</td>
<td>N N N</td>
<td>.</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>3.0</td>
<td>R</td>
<td>N</td>
<td>U</td>
<td>.</td>
<td>.</td>
<td>N A  .</td>
<td></td>
</tr>
</tbody>
</table>

APPENDIX 2

Summary Paragraph – (Long Abstract)

BACKGROUND & RESEARCH QUESTION: Similarities between the peripheral auditory and vestibular systems suggest that children with sensorineural hearing loss (SNHL) may demonstrate vestibular and balance impairments. This hypothesis was studied in 40 children with severe to profound SNHL and unilateral cochlear implants (CI) with the following specific questions in mind:

1. What is the relationship between sensorineural hearing loss (SNHL) and vestibular end organ and balance function in children?
2. What influence does etiology have on this relationship?
3. Can vestibular end organ function be correlated to performance on tasks of static and dynamic balance?
4. Does cochlear implantation alter vestibular end organ function?

METHODS: Vestibular function testing included an assessment of horizontal canal function in response to both a caloric and a rotational stimulus as well as an assessment of saccular function as measured by the vestibular evoked myogenic potential (VEMP). Static and dynamic balance was assessed with an age standardized functional test (Balance Subset of the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)). RESULTS: Horizontal semicircular canal function was abnormal in response to a caloric stimulus in 53% (17/32), with a large proportion of those (7/17 (41%)) reflecting mild to moderate unilateral abnormalities. In comparison, horizontal semicircular canal function in response to rotation was abnormal in 39% (14/36). Saccular function was absent bilaterally in 5/26 (19%) and unilaterally in 5/26 (19%) as measured by the VEMP. Significant differences in horizontal canal and saccular function were not seen between the implanted and non-implanted side although further evaluation is required. Age standardized balance abilities were significantly poorer ($\mu=12.9\pm5$(SD)) than normal hearing controls ($\mu=17\pm5$(SD); $p=0.0006$) and correlated best with horizontal canal function measured by rotational stimulation ($p=0.004;R^2=0.24$). SNHL due to meningitis or cochleovestibular anomalies was associated with worse vestibular and balance function.
compared with other etiologies. CONCLUSIONS: Overall, vestibular and balance dysfunction occurred in 38 to 53% of children with SNHL and CI, and is highly dependent on the etiology. In the current study, vestibular end-organ function was not significantly affected by cochlear implantation. While children with SNHL due to meningitis have little residual vestibular end-organ function and perform poorest on standardized tests of balance, they remain able to carry out their activities of daily living without compromise. Although compliance with all tests was high, rotational chair testing, which assesses higher frequency motion (0.25 to 5Hz) and thus more ‘real world’ vestibular function, correlated best with static dynamic balance. For this reason, rotational chair testing may represent the test of choice in this population, particularly given that it is amenable to testing children of all ages.
## APPENDIX 3

<table>
<thead>
<tr>
<th></th>
<th>HORIZONTAL CANAL</th>
<th>SACCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CALORIC</td>
<td>ROTATIONAL</td>
</tr>
<tr>
<td>MENINGITIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>ABNORMAL COCHLEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>CONNEXIN 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>36%</td>
</tr>
</tbody>
</table>

![Graphical representation of vestibular end-organ (dys)function as measured by caloric, rotational and VEMP testing. Results are categorized by etiology of SNHL.](image)

**Figure A.1.** Graphical representation of vestibular end-organ (dys)function as measured by caloric, rotational and VEMP testing. Results are categorized by etiology of SNHL.
A Test of Static and Dynamic Balance Function in Children With Cochlear Implants

The Vestibular Olympics

Sharon L. Cushing, MD; Ruth Chia, MSc, AuD(C); Adrian L. James, MA, BM, BCh, FRCS, FRCS(ORL-HNS); Blake C. Papin, MD, FRCS; Karen A. Gordon, PhD

Objectives: To determine the incidence of static and dynamic balance dysfunction in a group of children with profound sensorineural hearing loss receiving a cochlear implant and to assess the impact of cochlear implant activation on equilibrium.

Design: Observational cross-sectional study of children with single-sided implants, tested under 2 conditions: (1) implant on and (2) implant off in a random order.

Setting: Ambulatory setting within an academic, tertiary care children’s hospital.

Participants: Forty-one children (ages 4-17 years) with cochlear implants comprised the study group. Fourteen children with normal hearing served as controls.

Intervention: All participants performed a standardized test of static and dynamic balance function (Bruzulinks-Schetsky Test of Motor Proficiency 2 [BOT2] balance subset). Children with implants performed the BOT2 under the 2 randomized conditions.

Main Outcome Measures: Overall performance on the balance subset of the BOT2 and the influence of implant activation on performance.

Results: The mean (SD) age-adjusted scale score for our control group was 17.5 (5) points (95% confidence interval [CI], 14-20), which was not significantly different (P = .15) from the published age-adjusted mean for the BOT2 balance subset 15.3 (5) points. The group that had undergone implantation, however, performed significantly more poorly 12.6 (1) points; 95% CI, 10-14) than either the control group or the published test mean (P = .004). Children with implants performed better with their implants on than with their implants off (mean [SD] difference, 1.3 [2.7] points; 95% CI, 0.3-2.3; P = .01).

Conclusions: Large differences exist in the balance ability of children with sensorineural hearing loss requiring cochlear implantation compared with age-matched controls. Implant activation, however, conferred a slight advantage in accomplishing balance-related tasks. These results substantiate the need to further quantify the baseline vestibular dysfunction of our study population of children with cochlear implants, as well as the impact of implant activation on the input and output of the vestibular system.


IT IS PLAUSIBLE THAT LESIONS LEADING TO SENSORINEURAL HEARING LOSS COULD ALSO CONTRIBUTE TO DYSFUNCTION OF THE VESTIBULAR END ORGANS. WE EXAMINED THIS POSSIBILITY IN THE PRESENT STUDY BY EXAMINING BALANCE FUNCTION IN CHILDREN WITH PROFOUND SENSORINEURAL HEARING LOSS WHO USE A COCHLEAR IMPLANT. THERE IS ALSO A POTENTIAL FOR INTERACTION BETWEEN THE ELECTRICAL STIMULATION PROVIDED BY THE IMPLANT AND BALANCE AND VESTIBULAR FUNCTION. WE INVESTIGATED THIS POTENTIAL BY MEASURING BALANCE WITH THE IMPLANT ON AND OFF IN A RANDOMIZED ORDER IN THESE CHILDREN.

A number of studies have sought to document baseline vestibular function prior to cochlear implantation. The consensus is that a considerable percentage of candidates for cochlear implantation show prooperative vestibular dysfunction. These studies have focused primarily on the adult population and in general document a considerable degree of associated vestibular loss (range, 25%-100% hypofunction). Fewer studies have included young children. To date, the largest cohort of children assessed in this fashion was reported by Buchman et al in 2004. Testing 22 children aged 2 to 16 years with bilateral caloric irrigation, rotational chair testing, and computerized dynamic posturography, they found that 68% of the children had vestibular hypofunction or ataxia prior to undergoing cochlear implantation.
The same studies examined postoperative vestibular function in a similar fashion with the aim of determining the impact of implantation on vestibular function. On a clinically positive note, reports of severe and/or permanent vestibular dysfunction are rare even in the setting of bilateral implantation. This is particularly true in the setting of pediatric implantation, with only 7 of 575 children at our institution (1.2%) experiencing notable but transient imbalance following cochlear implantation (S.L.C., A.L.J., B.C.P., and K.A.G., et al, unpublished data 2007). Buchman et al suggested that the reason for this may be the higher degree of vestibular dysfunction in implant candidates; in this case, only a small percentage of implant candidates would be at risk of a considerable vestibular loss following implantation. There is also a generally accepted but untested notion that children are more able to adapt to vestibular injury than adults, which, if true, would further decrease the likelihood of a longstanding uncompensated vestibular defect in children undergoing cochlear implantation.

In addition to the potential for vestibular injury at the time of surgery, cochlear implantation also carries the risk that the electrical current provided by the implanted array could spread beyond the auditory portion of cranial nerve VIII and stimulate the vestibular portion. Such activation could, on the one hand, be detrimental to vestibular function, there could, for example, be negative impacts of chronic electrical stimulation of the labyrinth or vestibular nerve fibers. On the other hand, however, electrical stimulation of the vestibular system could theoretically provide some usable vestibular cues. Reports of vestibular sensations elicited by implant use are present, although infrequent.10-12 There are also reports of improved vestibular function postoperatively, especially in balance assessment using computerized dynamic posturography and particularly in the setting in which the implant is on and activated in noise.13-16

These clinical tests provide us with a partial but incomplete assessment of the function of the vestibular system. Balance equilibrium is maintained by a complex interplay among the visual, somatosensory, vestibular, and motor systems, and it is not uncommon to be faced with patients who are disabled by imbalance despite normal results from vestibular test battery. It was with this in mind that, for the purpose of the present study, we adopted a simple and standardized test of static and dynamic balance function in our assessment of children with cochlear implants.

The Borminck-Oserezkis Test of Motor Proficiency (BOT2) is a clinical test battery, first introduced in 1978, that has become the most widely used standardized measure of motor proficiency.13 It is most commonly employed within the realm of physical and occupational therapy and developmental psychology. It comprises a number of subtests, one of which is designed to assess overall balance function (the BOT2 balance subset). We applied the BOT2 to our cochlear implant population in the hope of addressing and answering the following questions: (1) Do children with profound sensorineural hearing loss receiving cochlear implantation perform differently on a test of static and dynamic balance function (BOT2) compared with their peers with normal hearing? (2) Do children with cochlear implants perform differently on a test of static and dynamic balance function when they have their implant on vs off?

<table>
<thead>
<tr>
<th>Table 1. Borminck-Oserezkis Test of Motor Proficiency Balance Subtest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance Subtest Item</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Standing with feet apart on a line</td>
</tr>
<tr>
<td>Walking forward on a line</td>
</tr>
<tr>
<td>Standing on 1 leg on a line</td>
</tr>
<tr>
<td>Walking forward heel to toe on a line</td>
</tr>
<tr>
<td>Standing on 1 leg on a balance beam</td>
</tr>
<tr>
<td>Standing heel to toe on a balance beam</td>
</tr>
</tbody>
</table>

**METHODS**

The study protocol was submitted, reviewed, and approved by the research ethics board at the Hospital for Sick Children, Toronto, Ontario. Written consent and verbal assent were obtained from the guardians and children, respectively.

Children with cochlear implants (hereinafter, the implant group) underwent a standardized test of static and dynamic balance function (the BOT2 balance subset). This was an observational cross-sectional study in which children with single-sided implants were tested under 2 conditions, (1) implant on and (2) implant off, in a random order. Although the test provides age-matched normative scores for the BOT2 balance subset, a group of children with normal hearing were tested as controls to estimate the uniformity and replication of the testing environment. Children with coexisting uncompensated visual loss or motor deficits were excluded from the study.

The BOT2 balance subset includes 9 separate tasks, of which 4 are performed with eyes open, then eyes closed (Table 1). The raw score is converted into a point score, and the point scores of the 9 separate tasks are summed to produce a total point score (range, 0-37 points). The total point score and the subject’s age at the time of testing are then used to look up an age-matched scale score based on the population norms data provided by the test (range, 1-35 points). The test was administered by 1 of 3 individuals (S.L.C., R.C.G., and K.A.G.) in 2 settings. Approximately half the implant group (n = 22) and all the controls were recruited at our annual cochlear implant picnic (total, 36 individuals). The remaining subjects were tested in our clinic (n = 19).

An independent t test was used to determine the significance of differences between the implant group (in the implant on condition) and both our own control group and the normative population mean provided with the test. A paired t test was used to determine the significance of differences within the implant group under the 2 conditions (implant on vs off). Data obtained in each of the subtests were assessed using a repeated measures analysis of variance (ANOVA) to determine the influence of vision and the presence of a balance beam on the balance function of our control and implant groups. A similar analysis was also performed to determine the relative influence of vision, the presence of a balance beam, and the implant status (on vs off) on the balance function within our implant group. We used SPSS (version 14.0, SPSS Inc, Chicago, Illinois) and SAS (version 9.1; SAS Inc, Cary, North Carolina) software for the statistical analyses.
RESULTS

Thirty-two children with single-sided implants were tested under 2 randomization conditions: (1) implant on and (2) implant off. An additional 9 children completed the BOT2 with their implant on only (total in implant group, 41). Fourteen children without implants were tested to serve as controls. Demographics of the study group are presented in Table 2. There was a roughly equal sex distribution within the control group (8 of 14 were female (57%) and a slight male predominance within the implant group (16 of 41 were female (40%)). The mean age of the children in the control group was 8 years vs 10 years for children in the implant group. This difference in age across groups was considered significant (t120=2.03, P =.05; unequal variances assumed). The duration of implant use varied from 2.3 to 12.3 years (mean [SD], 4.8 [1.2]). The mean (SD) age at implantation was 4.7 (3.6) years. All children were implanted unilaterally with a Nucleus 22, 24M, 24RCS, 24CA, 24KE, or Freedom device (Cochlear Corp, Melbourne, Australia).

LOOKING AT BALANCE IN CHILDREN WITH IMPLANTS

The published age-adjusted mean (SD) score (n=1320 children who participated in the group that established the normative means for the test) for the BOT2 balance subset is 15 (5) points (range, 1-35 points). In comparison, the mean score of our control group of children with normal hearing (n=14) was 17 (5) points. There was no statistically significant difference between our control group and the published normative data (t125=1.52; P =.15; unequal variances assumed Pr > F <.005). In comparison, the mean score for the implant group was 12 (6). The difference between the implant group and both the normative and control groups was statistically significant (t125=3.37; P =.002; unequal variances assumed Pr > F <.005; t125=2.95; P =.005; unequal variances assumed Pr > F <.005, respectively).

In a pair-wise comparison of the implant group (n=32) under the conditions of implant on vs off, subjects performed better with their implant on (mean [SD], 12 (6) points) than with their implant off (10 (5) points) (t31=2.68, P =.01).

IMPACT OF DURATION OF IMPLANT USE AND LEVEL OF DIFFICULTY ON BALANCE

The impact of age, age at implantation, duration of implant use, and etiology of hearing loss were examined using a linear regression model. On univariate analysis, only duration of implant use was a significant predictor of overall performance (F3,39=8.87; P =.005).

A repeated-measures ANOVA was used to assess the effects of vision (eyes open vs closed), balance beam (test with vs without a balance beam), and group (implant vs no implant) on BOT2 balance subset scores. Age was considered to be a covariate. The results of this analysis are detailed in Table 3. The clearest effect was for vision: all children performed significantly worse on an identical task with their eyes closed vs open (F =.003). However, the decrement in balance ability that occurred with eyes closed was similar for both the control and implant groups, as shown by the lack of significance of the interaction between eyes and group (F =.88). No other factors had significant effects on balance subset scores.

A repeated-measures ANOVA was also performed on data from the implant group only. The details of this analysis are shown in Table 4. We found that again visual status (eyes open vs closed) significantly affected balance scores (F =.007). In addition, the implant group had significantly greater difficulties balancing on the balance beam when their eyes were closed (F =.03). The balancing skills of young children deteriorated more than those of older children, on vs off the balance beam (age * balance beam interaction [where the asterisk indicates the balance beam age interaction in the regression model]; F =.04). Mean (SE) data for the BOT2 balance subset scores on vs off the balance beam with eyes opened vs closed are plotted in the Figure. The balance beam was particularly difficult for children with implants when their eyes were closed vs open (there was a significant interaction between visual status and presence of a balance beam [F =.03] and age, visual status, and presence

<table>
<thead>
<tr>
<th>Table 2. Demographics of Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>At implantation</td>
</tr>
<tr>
<td>Duration of implant use, y</td>
</tr>
<tr>
<td>Male:female ratio</td>
</tr>
<tr>
<td>Etiology of hearing loss, % (proportion)</td>
</tr>
<tr>
<td>Cochlear implant</td>
</tr>
<tr>
<td>Unknown etiology</td>
</tr>
</tbody>
</table>

* A total of 19 of 41 children (46%) had congenital, prelingual deafness, whereas 2 of 41 (5%) had progressive prelingual deafness.

<table>
<thead>
<tr>
<th>Table 3. Repeated-Measures ANOVA on Balance Scores*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>Balance beam (present vs absent)</td>
</tr>
<tr>
<td>Balance beam * age, y</td>
</tr>
<tr>
<td>Balance beam * group</td>
</tr>
<tr>
<td>Eyes (open vs closed)</td>
</tr>
<tr>
<td>Eyes (open vs closed) * age, y</td>
</tr>
<tr>
<td>Eyes (open vs closed) * group</td>
</tr>
<tr>
<td>Balance beam * eyes (open vs closed) * age, y</td>
</tr>
<tr>
<td>Balance beam * eyes (open vs closed) * group</td>
</tr>
</tbody>
</table>

* Abbreviations: ANOVA, analysis of variance; asterisk, the interaction between the designated variables in the regression model.

** For 41 children in the implant group using cochlear implants (n=22) who completed the BOT2 with implant on and off and an additional 9 who performed the BOT2 only with the implant on and 14 controls.

*Significance of the F <.05 level.
Table 4. Repeated-Measures ANOVA on Balance Scores

<table>
<thead>
<tr>
<th>Effect</th>
<th>F Value (Model)</th>
<th>F Value (Residual)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance beam (present vs absent)</td>
<td>0.12</td>
<td>2.30</td>
<td>0.14</td>
</tr>
<tr>
<td>Balance beam * age, y</td>
<td>4.06</td>
<td>2.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Eyes (open vs closed)</td>
<td>0.03</td>
<td>2.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Eyes (open vs closed) * age, y</td>
<td>0.11</td>
<td>2.30</td>
<td>0.14</td>
</tr>
<tr>
<td>Implant (on vs off)</td>
<td>0.02</td>
<td>2.30</td>
<td>0.08</td>
</tr>
<tr>
<td>Implant * age, y</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Balance beam * eyes (open vs closed)</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Balance beam * eyes (open vs closed) * age, y</td>
<td>4.06</td>
<td>2.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Balance beam * implant</td>
<td>0.11</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Balance beam * age, y</td>
<td>0.05</td>
<td>2.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Eyes (open vs closed) * implant</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Eyes (open vs closed) * implant * age, y</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Balance * eyes (open vs closed) * implant</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Balance * eyes (open vs closed) * implant * age, y</td>
<td>0.00</td>
<td>2.30</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Note: ANOVA analysis of variance: archer; the interaction between the designated variables in the regression model.

Significance at the P < .05 level.

Figure. Mean (SE) timed score (duration in seconds) for children with cochlear implants standing on 1 foot over 4 separate trials: (1) on balance beam (closed eyes); (2) off balance beam (closed eyes); (3) with eyes open; (4) with eyes closed. Cochlear implants were on and activated during all trials.

Our analysis demonstrates that children with cochlear implants performed poorly on our test of dynamic balance function compared with their peers with normal hearing but experienced some slight gains while wearing their cochlear implants. Like their hearing peers, children using cochlear implants performed better when they had their eyes open. The balance skills of children using implants also deteriorated significantly when they were on the balance beam with eyes closed (P = .03).

The results obtained for the control group were comparable with the published standardized norms for the test. This is important given that the test was administered outside of its usual context, a picnic ground vs an indoor waiting area. In addition, approximately 50% of the controls were the siblings of the children with hearing impairments, which presents the potential of introducing bias into the control group. Where possible, comparisons were made between the children with hearing impairments and the standardized norms, and the control group data were used as a comparison for task-specific analyses for which norms were not available.

This difference between children using cochlear implants and children with normal hearing was obvious and subjectively noted by all 3 examiners during each of the testing sessions. Certainly, this subjective observation was often also echoed by parents. When the children we tested were asked about their recreational activities, most were found to be able to ride bikes and skate; however, with more detailed inquiry, parents often stated that their children found such activities difficult (e.g., bike riding required training wheels for a prolonged period of time). Poor performance on the BOT2 was, however, not entirely uniform across the implant group. Several children in the implant group obtained scores at or above their age level. The difference between the implant and control groups, as well as within the implant group, may relate to the underlying etiology of the hearing loss, but this was not specifically addressed in the present study. In this study design we tested children only postoperatively and were unable to determine the relative contributions of deafness and implantation on performance on the BOT2. This question would be better answered by examining a paired fashion the performance of children on the BOT2 before and after implantation, a study that is currently under way.

In the implant group, the duration of implant use was a significant predictor of performance on the BOT2 (P = .005). However, the relationship was such that a shorter duration of implant use portended better performance. This seems to be the consequence of a small and heterogeneous subset of children with a short duration of implant use who perform quite well on the BOT2. This finding should likely be interpreted with caution, and further study is required to validate the relationship between duration of implant use and performance on the BOT2.

Visual cues seem to be equally important to the balancing abilities of both children with normal hearing and deaf children with cochlear implants. There were no significant interactions between vision and group (P = .88), suggesting little, if any, increased reliance on visual cues in children using cochlear implants. This is counter to the thought that children with hearing loss might rely more on visual cues than their hearing peers both to communicate and to balance.

The interaction effects found between the balance beam and both age and vision suggested that children using implants found the tasks on the balance beam particularly difficult. The effect of balance beam alone did not reach statistical significance (P = .095), but there was a trend toward deteriorating skills when on vs off the
balance beam. It is possible that the generally poor performance of children using cochlear implants on the balance beam tests limited the degree to which further determinations would be identified. Indeed, many children (n=18 [44%]) scored at minimum on the balance beam tasks.

Children with implants did demonstrate a small but significant improvement in their balance performance when they were wearing their implant (P<.01). This much smaller but significantly different balance function with the implant on vs off was not as reliably apparent to the testers on a subjective level (P=.01). However, anecdotal, many parents reported that they felt the children's balance improved markedly following cochlear implantation. It is impossible to tell whether the perceived benefits of an active implant on balance extend beyond the contribution of auditory cues alone. We did not control for the background noise level, and both conditions for testing (a picnic and a clinic waiting room) are ones in which certain degree of ambient noise would be expected. A future study might specifically address the role of auditory cues on the maintenance of equilibrium.

It is also possible that improvements in balance when the implant is worn are the result of electrical stimulation of the vestibular nerve. Electrical pulses delivered by a cochlear implant with the purpose of evoking an excitatory response within the auditory nerve may spread beyond their target, particularly at high levels of stimulation. The facial and vestibular nerves are at greatest risk. We have recently shown using objective measures that up to 30% of children with cochlear implants are at risk of facial nerve stimulation. In light of these findings, activation of the vestibular nerve and/or the vestibular end organs is a very real possibility. There are numerous reports within the literature describing discrete activation of the vestibular system leading to nystagmus and vertigo. In contrast to this discrete activation, perhaps is a low level of background vestibular activation that is responsible for the differences described herein and in other studies noting improvement in computerized dynamic posturography with the implant activated and in noise. In conclusion, we have demonstrated that large differences exist in the dynamic balance ability of children with sensorineural hearing loss requiring cochlear implantation compared with age-matched controls with normal hearing. Use of the implant, however, conferred an advantage in accomplishing balance-related tasks. These results substantiate the need to further quantify the baseline vestibular dysfunction of our implant group as well as the impact of activation on the input and output of the vestibular system. This will advance understanding of the pathophysiologic characteristics of cochlear vestibular loss, as well as the potential for acquired vestibular injury in the setting of bilateral cochlear implantation.

Submitted for publication: January 30, 2007; final revision received May 19, 2007; accepted June 13, 2007. Correspondence: Sharon L. Cushing, MD, Department of Otolaryngology-Head and Neck Surgery, University of Toronto, Hospital for Sick Children, Sixth Floor, 555 University Ave, Toronto, ON M5G 1X8, Canada (scushing@utoronto.ca).

Author contributions: Drs Cushing, Papsin, James, and Gordon and Ms Chia had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cushing, James, Papsin, and Gordon. Acquisition of data: Cushing, Chia, James, Papsin, and Gordon. Analysis and interpretation of data: Cushing, James, Papsin, and Gordon. Drafting of the manuscript: Cushing, James, and Gordon. Critical revision of the manuscript for important intellectual content: Cushing, Chia, James, and Papsin. Statistical analysis: Cushing and Gordon. Obtained funding: Cushing and Papsin. Administrative, technical, and material support: Cushing, Chia, and Gordon. Study supervision: Cushing, James, Papsin, and Gordon.

Financial disclosure: None reported.

Funding/support: Dr Cushing was supported by a fellowship grant from the Canadian Institute for Health Research and by the Champions Fund, Freeman, Friedberg Clinician Scientist Fund for the duration of the study.

Previous presentation: This article was presented at the American Society of Pediatric Otolaryngology 2007 Annual Meeting; April 27, 2007; San Diego, California.

Additional information: This study was awarded the Charles Ferguson Clinical Research Award for best peer-reviewed paper by a resident at The American Society of Pediatric Otolaryngology 2007 Annual Meeting. Additional contributions: Patricia Fuller, Vicky Papapachoanou, MSc, Audi O, and the Cochlear Implant Team and audiologists at the Hospital for Sick Children assisted in patient recruitment.

REFERENCES