Inner Ear Morphometry on High Resolution Computed Tomography in Patients with Sensorineural Hearing Loss

Dr. Javid Jahanbakhsh

Dissertation Submitted in Partial Fulfillment of the Requirement for The Degree of Master of Medicine (Radiology)

SCHOOL OF MEDICAL SCIENCES

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Key words: Inner Ear, Sensorineural Hearing Loss, Computed Tomography

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Introduction: Structural abnormality of inner ear structures found in high resolution CT scan in the patient with sensorineural hearing loss (SNHL) is well known, however this abnormalities only seen in 25 % of the patients. Recent developments in CT image acquisition raised the hypothesis that subtle different in the size of inner ear structures can be detected by measuring this structures on High resolution CT image. This can help the physicians in early diagnosis of SNHL.

Objectives: To compare the cochlear, vestibuler and lateral semicircular canal measurements between patients with sensorineural hearing loss (SNHL) patient and normal subjects using high resolution Computed Tomography (HRCT).

Materials and methods: A retrospective study was conducted from May 2012 till August 2015 in the Department of Radiology, Hospital Universiti Sains Malaysia. Patients with sensorineural hearing loss who was referred for computed tomography of the temporal bone were selected in the study group. All scans were performed on Siemens 128-slices CT scanner Somatom Definition 128-slice with high-resolution scanning protocol. All the images were reconstructed to bone window. Patient who had computed computed tomography of the temporal bone for other indications with normal contralateral ear were taken as a control group. Three inner ear structures (vestibular width, cochlear basal turn and lateral semicircular canal bony island width) were measured on axial image on diagnostic workstation). The measurements were repeated three times and average of these

measurements were taken. Measurements were randomly selected and validated by an experienced radiologist to minimize bias.

Results: Fifty ears from 28 patients with SNHL (22 patients with bilateral disease and 6 patients with unilateral) were included in this study. Gross abnormality of inner ear detected on HRCT in 5 ears (3 patients) of SNHL were excluded. A total of 45 ears were selected in both study and control groups. Twenty-five ears from patients with SNHL were male patient and 20 ears were female, same as control group. Age range for patients with SNHL was 2 to 23 years old with mean of 9.98 years old. The age range for control group was 2 to 76 years old with mean of 29.55 years. The mean (standard deviation) width of cochlear was 0.190 cm (0.017 cm), vestibular was 0.330 cm (0.039 cm) and lateral semicircular bone island width was 0.362cm (0.566 cm) of patients with SNHL. There were no significantly different of mean of these measurements with control group (*P* value > 0.05).

Conclusions: The morphometry of cochlear, vestibular and lateral semicircular bone island width are not reliably differentiating between SNHL and non SNHL patients.

PM Dr Mohd Ezane Aziz: Supervisor

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List of Abbreviations

CT …… Computed Tomography

CHL……Conductive Hearing Loss

FOV ……..Field of View

HRCT……..…High Resolution Computed Tomography

LSCC ……. Lateral Semicircular Canal

ORLHNS…….…...Otorhinolaryngology & Head and Neck Surgery

PACS…….…….……. Picture Archiving and Communication System

PSCC …….…...Posterior Semicircular Canal

PTA…….……...Pure-Tone Audiometry

SNHL ……...……..… Sensorineural Hearing Loss

SCC……. Semicircular Canal

SSCC…….…… Superior Semicircular Canal

VA……...……Vestibular Aqueduct

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ACKNOWLEDGEMENT

Thank you is the least I can say to all the individuals to show my appreciation for everything that they have done for me throughout the period of my dissertation project. Sincerest appreciation to my supervisor, PM Dr. Mohd Ezane Aziz (Lecturer and Radiologist, Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan) for his guidance and supervision. His exemplary knowledge and vast rich experience in the research field of radiology has greatly enlightened my myopic view. The kindness and patience that she has shown to me during this whole period has been a pillar of support for me.

I would also like to take this opportunity to convey my deepest gratitude to my First Supervisor Dr Norzila Tendot Abu Bakar**,** PM Dr.Dinsuhaimi sidek and all other lecturers of the Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia for their support of this dissertation project. Their patience, help and encouragement has helped to turn my dream of this dissertation into a reality. Sincerest thanks to PM Dr. Mohd Shafie Abdullah**,** Head of Department of Radiology at Hospital Universiti Sains Malaysia.

Finally, I thank with love to my parents. They were always supporting and encouraging me with their best wishes.

Last but not least, with love to my wife, Dr Asa Yazdani Fard who has loved, supported, encouraged and helped me get through this critical period in the most positive way.

ABSTRAK

Tujuan: Untuk membanding ukuran purata koklea, vestibul dan pulau tulang terusan lateral semicircular antara pesakit yang mengalami masalah kehilangan deria saraf pendengaran berbanding dan kumpulan kawalan menggunakan Skan CT beresolusi tinggi.

Bahan dan kaedah: Kajian retrospektif telah dijalankan dari Mei 2012 hingga Ogos 2015 di Jabatan Radiologi, Hospital Universiti Sains Malaysia. Pesakit hilang deria pendengaran yang dirujuk untuk skan CT beresolusi tinggi atau HRCT pemeriksaan tulang temporal telah diambil sebagai sampel. Semua pemeriksaan pengimbasan ini dilakukan dengan mesin CT skan 128-slice Siemens Somatom Definition, dengan protocol imbasan beresolusi tinggi. Kumpulan komalan diambil dari pesakit tanpa masalah hilang deria pendengaran yang menjalani skan CT tulang temporal dan mempunyai telinga kontralateral yang normal. Tiga struktur dalaman telinga dikenalpasti iaitu kelebaran vestibular, putaran basal koklea dan kelebaran pulau tulang terusan lateral semicircular, dan diukur mengikut ketetapan ke atas imej axial menggunakan stesen kerja diagnostik. Ukuran diambil sebanyak tiga kali dan purata ukuran telah digunakan. Ukuran telah dibuat oleh pakar radiologi secara rawak untuk tujuan validasi.

Keputusan: Sebanyak 50 telinga hilang pendengaran telah dimasukkan untuk kumpulan kajian (22 pesakit dengan hilang pendengaran kedua-dua belah dan 6 pesakit dengan hilang pendengaran sebelah). Sebanyak 5 subjek tidak diambil kira dalan kumpulan kajian kerana kecacatan telinga yang melampau. Hanya 45 bilangan telinga telah dipilih dalam kumpulan kajian dan 45 telinga dalam kumpulan kawalan. Purata ukuran kelebaran (sisihan piawai) koklear ialah 0.190 cm (0.017 cm), vestibul ialah 0.330 cm (0.039 cm), dan kelebaran pulau tulang lateral semicircular ialah 0.362 cm (0.566 cm) bagi pesakit yang hilang pendengaran. Ukuran kelebaran koklear, vestibular and pulau tulang lateral semicircular di tidak ada perbezaan yang signifikan dengan kumpulan kawalan (P <0.05).

Kesimpulan: Ukuran kelebaran koklear, vestibular and pulau tulang lateral semicircular tidak boleh dijadikan sandaran untuk membezakan telinga pesakit yang mengalami masalah kehilangan deria saraf pendengaran dengan pendegaran normal.

ABSTRACT

Purpose: To compare the cochlear, vestibuler and lateral semicircular canal measurements between patients with sensorineural hearing loss (SNHL) patient and normal subjects using high resolution Computed Tomography (HRCT).

Materials and methods: A retrospective study was conducted from May 2012 till August 2015 in the Department of Radiology, Hospital Universiti Sains Malaysia. Patients with sensorineural hearing loss who was referred for computed tomography of the temporal bone were selected in the study group. All scans were performed on Siemens 128-slices CT scanner Somatom Definition 128-slice with high-resolution scanning protocol. All the images were reconstructed to bone window. Patient who had computed computed tomography of the temporal bone for other indications with normal contralateral ear were taken as a control group. Three inner ear structures (vestibular width, cochlear basal turn and lateral semicircular canal bony island width) were measured on axial image on diagnostic workstation). The measurements were repeated three times and average of these measurements were taken. Measurements were randomly selected and validated by an experienced radiologist to minimize bias.

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Conclusions: The morphometry of cochlear, vestibular and lateral semicircular bone island width are not reliably differentiating between SNHL and non SNHL patients.

INTRODUCTION

The sensorineural hearing loss (SNHL) may be due to genetic cause or sequelae of infection or injury at birth, however in some cases, no specific cause is detectable. Congenital sensorineural hearing loss (SNHL) affects 4 to 11 per 10 000 children (Bergstrom, 1980). It may arise as a result of abnormalities in the inner ear structures, the vestibulocochlear nerve, or the processing centers of the brain located at the cortex of the temporal lobe. During the past decade, high-resolution computed tomography (HRCT) has been thought to be the best imaging study to evaluate inner ear abnormalities, including anatomic variances of the bony portion of the temporal bone. It allows excellent depiction of the intricate osseous anatomy and malformations of the inner ear.

Abnormalities of the cochleovestibular complex have long been associated with congenital SNHL. Although severe malformations such as complete labyrinthine aplasia, cochlear aplasia, and common cavity deformity are typically identified by visual inspection alone, this abnormalities represent only 25% of radiographic abnormalities found in patients with SNHL (Jackler *et al*., 1987). Visual inspection is often inadequate for identification of subtle abnormalities such as lateral semicircular canal dysplasia and mild cochlear hypoplasia. Up to one third of these less severe malformations are missed by simple visual inspection (Purcell *et al*., 2003a).

Recently, some articles described the association of minor variances of the temporal bone, such as a small lateral semicircular bone island and dilated cochlea and vestibule with SNH (Purcell *et al*., 2003b). However, the exact size that constitutes an enlarged vestibule has been debated. A classification scheme for malformations had been developed by Jackler in 1987 and revisited by Sennaroglu in 2002, who differentiates the Mondini malformations (IP-II) from the cystic cochlea (IP-I) (Sennaroglu and Saatci, 2002) as in figure 1.

1. **Literature Review**

Development of the inner ear

Development of the inner ear begins early during embryogenesis. By the end of the eighth week, the membranous labyrinth has assumed its characteristic convoluted shape. Gradual ossification of the otic capsule develops around the membranous labyrinth and is essentially complete by birth. Maturation of the sensory epithelium occurs long after formation of the membranous labyrinth, during the late second and early third trimester. By the twenty-sixth to twenty-eighth week of gestation, hair cell and auditory neural development are largely complete. Thus, the normal human fetus may be able to hear 2.5 to 3 months before birth (Jackler *et al.*, 1987)**.**

Adult size is achieved in the inner ear labyrinth by approximately 25 weeks' gestation, and minimal variability in age, sex, side, and race is found after birth (Elias *et al*, 1998). Inner ear volumetric measurements showed no meaningful size difference among different age related experimental groups from 6 month of age and older (Jackler *et al*., 1987) (Pelliccia *et al*, 2014).

Most inner ear malformations arise when there is interruption in formation of membranous labyrinth during first trimester of pregnancy (Fig 2.1). They can be considered in two broad categories: malformations with pathologic changes limited either to the membranous labyrinth or malformations that involve both the osseous and membranous part. This division has been chosen because of its clinical relevance. Only patients with malformed otic capsules have abnormal inner ear radiographs and therefore may be diagnosed during life. In a series of patients with radiographically detectable malformations of the inner ear, the cochlea was involved in 76%, the semicircular canals in 39%, and the vestibular aqueduct in 32% of ears (Jackler *et al*., 1987). By inference, those children with congenital SNHL and radiographically normal inner ears may be assumed to possess anomalies limited to the membranous labyrinth or neural pathways (Jackler *et al*., 1987).

Classification of Inner Ear Dysplasia

A classification scheme for malformations had been developed by Jackler in 1987 and revisited by Sennaroglu in 2002, who differentiates the Mondini malformations (IP-II) from the cystic cochlea (IP-I) (Sennaroglu and Saatci, 2002).

Cochlear malformations include the following:

1) Michel deformity:
   There is complete absence of all cochlear and vestibular structures (Fig.2a).
2) Cochlear aplasia:
   The cochlea is completely absent (Fig 2b).
3) Common cavity deformity:
   There is a cystic cavity representing the cochlea and vestibule, but without showing any differentiation into cochlea and vestibule (Fig 2c).
4) Cochlear hypoplasia:
   Malformation is further differentiated so that the cochlea and vestibule are separated from each other but their dimensions are smaller than normal. Hypoplastic cochlea resembles a small bud off the internal auditory canal (Fig 2d).
5) Incomplete partition type I (IP-I):
   The cochlea is lacking the entire modiolus and cribriform area, resulting in a cystic appearance. This is accompanied by a large cystic vestibule (Fig 2e).
6) Incomplete partition type II (IP-II) (Mondini deformity):
   The cochlea consists of 1.5 turns, in which the middle and apical turns coalesce to form a cystic apex, accompanied by a dilated vestibule and enlarged vestibular aqueduct (VA) (Fig 2f).

A more recent classification, proposed by Steel *et al*., and based on animal models, has subdivided the histopathology of inner ear disorders into three separate groups: morphogenetic, neuroepithelial, and cochleosaccular (Steel *et al*., 1987). Structural abnormalities affecting both the osseous and the membranous labyrinth of the inner ear are referred to as morphogenetic. Malformations limited to the membranous labyrinth without bony abnormality are thought to represent the largest number of cases and are further subdivided into neuroepithelial degeneration and cochleosaccular degeneration (Steel *et al*., 1987).

On the other hand, pre-mortem detection of membranous abnormalities remains difficult. The hearing loss is attributed to malformations of the membranous labyrinth for the 75 to 80% of radiologic studies deemed normal by visual inspection and/or measurement. However, it is likely that this group is heterogeneous, including patients with entirely normal bony labyrinths as well as patients with very subtle abnormalities below the threshold of malformation detectable with current CT technology.

Several authors have investigated subtle anatomical variations within the normal range for potential relationships with hearing loss. These studies describe measurements of multiple inner ear structures for the purpose of describing the normative data for quantification of the inner ear, and to quantitatively classify anatomic anomalies described by Jackler and Sennaroglu (Jackler *et al*., 1987).

Our study attempted to evaluate subtle bony morphology abnormalities of the inner ear structures in patients with SNHL who are regarded to be normal in appearance on HRCT that will aid early diagnosis of SNHL. Measurement of inner ear structures using new CT scan technology can be helpful to identify subtle abnormalities of inner ear in patient with SNHL which cannot be detected by visual inspection. Based on available studies, till today, there is no conclusive result regarding the role of measurements of inner ear structures in predicting SNHL. Consequently, there have been efforts to develop a standardized measurement that can be used as an effective way in diagnosing patients.

2. Rationale of the Study

Measurement of inner ear structures using new CT scan technology can be helpful to identify subtle abnormalities of inner ear in patient with SNHL which cannot be detected by visual inspection. Consequently, there have been efforts to develop a standardized measurement that can be used as an effective way in diagnosing patients. Definite conclusions will aid early diagnosis of SNHL.

Based on available studies, till today, there is no conclusive result regarding the role of measurements of inner ear‘s structures in predicting SNHL.

STUDY PROTOCOL

Objectives:

General Objective

To evaluate the morphology of cochlea, vestibule and lateral semicircular canal in SNHL patient on high resolution CT.

Specific Objectives

1- To compare mean vestibular width between SNHL patients and control group

2- To compare mean cochlear basal turn width between SNHL patients and control group

3- To compare mean lateral semicircular canal (LSCC) bony island width between SNHL patients and control group.

Methodology

Study Design

A retrospective case control study was conducted in Hospital Universiti Sains Malaysia, Kubang Kerian from May 2012 till November 2015. Patients who had HRCT scan of the temporal bone in Department of Radiology from 1st May 2009 till 30th August 2015 were searched from GE Centricity Picture & Archiving System (PACS), and medical record of these patients were reviewed.

All patients (6 months old or above) who were diagnosed to have unilateral or bilateral SNHL by otorhinolaryngologist and had bone-conduction and air-conduction thresholds within 10 dB of each other, and thresholds are higher than 25 dB on pure-tone audiometry (PTA) examination were selected as study sample. Patients referred for temporal HRCT due to reasons other than conditions involving inner air such as unilateral cholestatoma, infection or trauma were included for control group. Since these conditions are mostly manifest unilaterally, the contralateral ear with normal hearing condition confirmed by careful review of medical record (including PTA) were taken. Patients with abnormal or suspicious

involvement of inner ear structures in normal side of ear detected after reviewing HRCT images were excluded.

Based on literatures, there is little variability with age for dimensions of the human inner ear's structures (Johnson and Lalwani, 2000) (except the IAC that is not included in our study). So the variety of age in this study was ignored.

Independent T-Test was performed to compare the measurements of the two groups.

Ethical approval

Ethical permission have been obtained from Human Research Ethics Committee, number: JEPeM/283.3. (1.7), USM (Appendix A). The study used secondary data and patients were not directly involved. Consequently, consent form from the patients was not necessary. However, permission was obtained from hospital director to use CT images. Patients' identities remained confidential and anonymous.

Sampling Method

Sample size calculation

PS software (Dupont and Plummer, 1997) was used to calculate the sample size based on comparing two means. To detect the difference of 0.2 between groups, SD was estimated equal to 0.26 within each subject groups using the previous study (Lan *et al*., 2009). 45 experimental subjects and 45 control subjects were required to reject the null hypothesis with probability (power) 0.95. Type I error probability associated with this test of this null hypothesis is 0.05.

Reference population

All Malaysian patients who underwent HRCT of temporal bone in Department of Radiology, Hospital Universiti Sains Malaysia (Hospital USM).

Inclusion criteria

A- Study Group:

All the patients above 6 month old, with unilateral or bilateral SNHL that referred from Otorhinolaryngology- Head and Neck Surgery (ORL-HNS) clinic for HRCT of temporal bone. There was no specific age considered as an upper limit in this history.

B- Control Group:

The normal ear of patients above 6 month old without any clinical history of hearing loss at the same side that will undergo HRCT of temporal bone (for acquired diseases involving other ear) in Department of Radiology, Hospital USM. Common indications are cholesteatoma, otitis media and trauma. All the patients with suspicious involvement of inner ear structures at HRCT in normal side of ear will be excluded later after reviewing HRCT images.

Exclusion criteria

A- Study Group ;

- Patients with any other disease involving inner ear structures like tumors if incidentally be found in reviewing of the HRCT images.

- Patients with grossly obvious inner ear abnormality on HRCT, based on the Jackler *et al* classifications (Jackler *et al.*, 1987). (Designated areas are not measurable due to incomplete formation or distorted structures)

- Poor quality of images that hinder for interpretation (due to motion, metal or others artifacts)

B- Control Group:

Based on history and after reviewing CT scans

-Patient with visually obvious deformity of the temporal bone or skull

-Patient with previous operation of temporal bone

-Patients who involved with traumatic fracture of temporal bone

-Patients with space occupying lesion or mass involving temporal bone

-Poor quality of images that hinder for interpretation (due to motion, metal or others artifacts)

Source of populations

This study was conducted in Hospital Universiti Sains Malaysia. HRCT was used for the patients referred to Department of Radiology for temporal bone HRCT scan.

Obtain data

Designated inner ear structures were measured by the researcher. Data were obtained from temporal bone computed tomography images from the normal and SNHL groups using a computer-based caliper that forms part of a Picture Archiving and Communication System (PACS). The measurements was made by the study performer, using a computer-based caliper on a 512 x 512 pixel image under a window level of 700 HU and a window width of 4,000 HU. This is the best conditions showing low attenuation of inner ear structure. The measurements were repeated three times and mean of measurements were registered for each sample. Second assessment were made by an independent experienced radiologist for thirty percent of randomly selected patient. Data were validated using Independent T test comparing two means.

Three identifiable inner ear structures were measured in designated areas on axial plan via PACS; vestibular width, cochlear basal turn and lateral semicircular canal (LSCC) bony island width (Fig 3.1 a, b, c and d) **.**

Cochlea was identified as a spiral tubular structure within temporal bone with soft tissue density within adjacent to the blind end of internal auditory canal. Its axis is vertically oriented with the base at below. On the CT scan images maximum Cochlear basal turn width measured as a distance between its bone edges on axial plan among the slices displaying it at the line perpendicular to middle of its long axis (Fig 3.1 a and d).

Vestibule is a secular structures within temporal bone with soft tissue density within connected to the semicircular canals. Its maximum width measured as distance between two bone edge among the slices displaying it in the middle of line perpendicular to its longitudinal axis (Fig 3.1 b and d). Lateral semicircular canal is one of three semicircular canals that located in axial plan, lateral to the vestibule. Maximum diameter of its bony island measured as the distance of two bone edge among the slices displaying it in the line perpendicular to long vestibular axis (Fig 3.1 c and d). All measurement are taken on axial plane.

CT scan Protocol

All scans were performed on 128-slices Siemens Somatom Definition CT scanner. The imaging protocol were used for HRCT temporal bone with zero gantry angle, 120 kV and effective 230 mAs, slice thickness of 0.4 mm, pitch of 0.85, field of view (FOV) of 189 mm and with a high-resolution bone algorithm covering whole petrous pyramid bone. All the images were reformatted to bone window (Kernel H70h Syngo, Siemens) at CT console and then were sent to PACS storage.

CT Images of temporal bone were analyzed using GE PACS Universal Viewer (version 6) on diagnostic workstation with 2-Megapixel 21-inches greyscale monitor. The measurement of the vestibular width, cochlear basal turn width and lateral semicircular canal bony island width were made using a computer-based caliper on a 512 x 512-pixel image and zoom factor of 2.3 under a window level of 700 HU and a window width of 4,000 HU. This is the best conditions showing low attenuation of inner ear structures. Three identifiable inner ear structures were measured in designated slice on axial plane (Fig 3)**.**

Validation

Validation of these measurements were made by an independent experienced radiologist using thirty percent of randomly selected samples using Interclass correlation (ICC) (*Appendix B*). Mean and Standard Deviation (SD) of were calculated for the vestibular width, cochlear basal turn width and lateral semicircular canal bony island width. Independent T-test statistical test was used to compare the mean width of determined inner ear structures and α will be taken at 5%.

ETHICAL APPROVAL

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

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Date of meeting: 28 April 2014
Venue : Meeting Room, Centre for Research Initiatives, Clinical and Health Sciences, USM Kampus Kesihatan.
Time : 9.00 a.m – 1.30 p.m
Meeting No : 283

Members of the Sub Committee of the Human Research Ethics Committee, Universiti Sains Malaysia who reviewed the protocol/documents are as follows:

Member (Title and Name)		Occupation (Designation)	Male/ Female (M/F)	Tick (✓) if present when above items, were reviewed
Deputy Chairperson : Professor Dr. Mohd Shukri Othman		Deputy Chairperson of Human Research Ethics Committee	M	✓ (Deputy Chairperson)
Secretary: Mr. Mohd Bazlan Hafidz Mukrim		Research Officer	M	✓
Members :				
1.	Dato' Hj. Ellias Zakaria	Lecturer, School of Humanity	M	✓
2.	Professor Wan Abdul Manan Wan Muda	Lecturer, School of Health Sciences	M	✓
3.	Associate Professor Dr. Mohtar Ibrahim	Lecturer, School of Medical Sciences	M	✓
4.	Associate Professor Siti Hawa Ali	Lecturer, School of Health Sciences	F	✓
5.	Dr. Teguh Haryo Sasongko	Lecturer, School of Medical Sciences	M	✓
6.	Dr. Haslina Taib	Lecturer, School of Dental Sciences	F	✓
7.	Tn. Hj. Ismail Hassan	Community Representative	M	✓

The Human Research Ethics Committee of Universiti Sains Malaysia is in compliance with International Conference on Harmonization–Guidelines for Good Clinical Practice (ICH-GCP) guidelines and Declaration of Helsinki.

PROFESSOR DR. MOHD SHUKRI OTHMAN
Deputy Chairperson
Human Research Ethics Committee

UNIVERSITI SAINS MALAYSIA

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

Our. Ref. : USM/JEPeM/283.3.(1.7)
Date : 5th June 2014

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The Human Research Ethics Committee, Universiti Sains Malaysia (FWA Reg. No: 00007718; IRB Reg. No: 00004494) has approved in principle the study mentioned below:

Title	Morphometry of Cochlea, Vestibule and Lateral Semicircular Canal in Sensorineural Hearing Loss Patient on High Resolution CT.		
Protocol No	-	**Principle Investigator**	Dr. Javid Jahanbakhsh
Date of approval Protocol received Reviewed by Committee Received Amended Protocol	5th June 2014 30th January 2014 16th April 2014 21st April 2014	**Co-Investigator(s)**	Dr. Rohsila Muhamad Prof. Dr. Dinsuhaimi Sidek Dr. Ahmad Helmy Abdul Karim
Research Center	Hospital Universiti Sains Malaysia.	**Date of study start**	June 2014 – May 2016
Financial Support	-	**Number of Samples**	54 samples

The following item (✓) have been received and reviewed:-

(✓) **Ethical Approval Application Form**
(✓) **Research Proposal**
(✓) **Data Acquisition Form**

Investigator(s) are required to:
a) follow instructions, guidelines and requirements of the Human Research Ethics Committee, Universiti Sains Malaysia (JEPeM)
b) report any protocol deviations/violations to Human Research Ethics Committee (JEPeM)
c) comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki
d) note that Human Research Ethics Committee (JEPeM) may audit the approved study.

PROFESSOR DR. MOHD SHUKRI OTHMAN
Deputy Chairperson
Human Research Ethics Committee

MANUSCRIPT

INTRODUCTION

The sensorineural hearing loss (SNHL) may be due to genetic cause or sequelae of infection or injury at birth, however in some cases, no specific cause is detectable. Congenital sensorineural hearing loss (SNHL) affects 4 to 11 per 10 000 children (Bergstrom, 1980). It may arise as a result of abnormalities in the inner ear structures, the vestibulocochlear nerve, or the processing centers of the brain located at the cortex of the temporal lobe. During the past decade, high-resolution computed tomography (HRCT) has been thought to be the best imaging study to evaluate inner ear abnormalities, including anatomic variances of the bony portion of the temporal bone. It allows excellent depiction of the intricate osseous anatomy and malformations of the inner ear.

Development of the inner ear begins early during embryogenesis. By the end of the eighth week, the membranous labyrinth has assumed its characteristic convoluted shape. Gradual ossification of the otic capsule develops around the membranous labyrinth and is essentially complete by birth. Maturation of the sensory epithelium occurs long after formation of the membranous labyrinth, during the late second and early third trimester. By the twenty-sixth to twenty-eighth week of gestation, hair cell and auditory neural development are largely complete. Thus, the normal human fetus may be able to hear 2.5 to 3 months before birth (Jackler *et al.*, 1987)**.**

Adult size is achieved in the inner ear labyrinth by approximately 25 weeks' gestation, and minimal variability in age, sex, side, and race is found after birth (Elias *et al*, 1998). Inner ear volumetric measurements showed no meaningful size difference among different age related experimental groups from 6-month of age and older (Jackler *et al*., 1987) (Pelliccia *et al*, 2014). Most inner ear malformations arise when there is interruption in formation of membranous labyrinth during first trimester of pregnancy (Fig 2.1). They can be considered in two broad categories: malformations with pathologic changes limited either to the membranous labyrinth or malformations that involve both the osseous and membranous part. This division has been chosen because of its clinical relevance. Only patients with malformed otic capsules have abnormal inner ear radiographs and therefore may be diagnosed during life. In a series of patients with radiographically detectable malformations of the inner ear, the

cochlea was involved in 76%, the semicircular canals in 39%, and the vestibular aqueduct in 32% of ears (Jackler *et al*., 1987). By inference, those children with congenital SNHL and radiographically normal inner ears may be assumed to possess anomalies limited to the membranous labyrinth or neural pathways (Jackler *et al*., 1987).

Abnormalities of the cochleovestibular complex have long been associated with congenital SNHL. Although severe malformations such as complete labyrinthine aplasia, cochlear aplasia, and common cavity deformity are typically identified by visual inspection alone, this abnormalities represent only 25% of radiographic abnormalities found in patients with SNHL (Jackler *et al*., 1987). Visual inspection is often inadequate for identification of subtle abnormalities such as lateral semicircular canal dysplasia and mild cochlear hypoplasia. Up to one third of these less severe malformations are missed by simple visual inspection (Purcell *et al*., 2003a).

Recently, some articles described the association of minor variances of the temporal bone, such as a small lateral semicircular bone island and dilated cochlea and vestibule with SNHL (Purcell *et al*., 2003b). However, the exact size that constitutes an enlarged vestibule has been debated. A classification scheme for malformations had been developed by Jackler in 1987 and revisited by Sennaroglu in 2002, who differentiates the Mondini malformations (IP-II) from the cystic cochlea (IP-I) (Sennaroglu and Saatci, 2002) as in Figure 1.

Cochlear malformations include the following:

1) Michel deformity:
   There is complete absence of all cochlear and vestibular structures (Fig.2a).
2) Cochlear aplasia:
   The cochlea is completely absent (Fig 2b).
3) Common cavity deformity:
   There is a cystic cavity representing the cochlea and vestibule, but without showing any differentiation into cochlea and vestibule (Fig 2c).
4) Cochlear hypoplasia:
   Malformation is further differentiated so that the cochlea and vestibule are separated from each other but their dimensions are smaller than normal. Hypoplastic cochlea resembles a small bud off the internal auditory canal (Fig 2d).
5) Incomplete partition type I (IP-I):

The cochlea is lacking the entire modiolus and cribriform area, resulting in a cystic appearance. This is accompanied by a large cystic vestibule (Fig 2e).

6) Incomplete partition type II (IP-II) (Mondini deformity):
   The cochlea consists of 1.5 turns, in which the middle and apical turns coalesce to form a cystic apex, accompanied by a dilated vestibule and enlarged vestibular aqueduct (VA) (Fig 2f)

A more recent classification, proposed by Steel *et al*., and based on animal models, has subdivided the histopathology of inner ear disorders into three separate groups: morphogenetic, neuroepithelial, and cochleosaccular (Steel *et al*., 1987). Structural abnormalities affecting both the osseous and the membranous labyrinth of the inner ear are referred to as morphogenetic. Malformations limited to the membranous labyrinth without bony abnormality are thought to represent the largest number of cases and are further subdivided into neuroepithelial degeneration and cochleosaccular degeneration (Steel *et al*., 1987).

On the other hand, pre-mortem detection of membranous abnormalities remains difficult. The hearing loss is attributed to malformations of the membranous labyrinth for the 75 to 80% of radiologic studies deemed normal by visual inspection and/or measurement. However, it is likely that this group is heterogeneous, including patients with entirely normal bony labyrinths as well as patients with very subtle abnormalities below the threshold of malformation detectable with current CT technology.

Several authors have investigated subtle anatomical variations within the normal range for potential relationships with hearing loss. These studies describe measurements of multiple inner ear structures for the purpose of describing the normative data for quantification of the inner ear, and to quantitatively classify anatomic anomalies described by Jackler and Sennaroglu (Jackler *et al*., 1987).

Based on previous studies there were various measurement methods to evaluate inner ear structures. Lan *et al.* (2009) had used 10 different measurements of inner ear structures to study inner ear in patient with SNHL. Purcell *et al*. (2003) measured 25 different areas to establish a normative cochlear and vestibular size on axial and coronal plane.

Our study attempted to evaluate subtle bony morphology abnormalities of the inner ear structures in patients with SNHL who are regarded to be normal in appearance on HRCT that will aid early diagnosis of SNHL. Measurement of inner ear structures using new CT scan technology can be helpful to identify subtle abnormalities of inner ear in patient with SNHL which cannot be detected by visual inspection. Based on available studies, till today, there is no conclusive result regarding the role of measurements of inner ear structures in predicting SNHL. Consequently, there have been efforts to develop a standardized measurement that can be used as an effective way in diagnosing patients.

The objectives of this study are to compare the vestibular width, cochlear basal turn width and lateral semicircular canal bony island width between SNHL patients and normal hearing patients without gross structural abnormality.

METHODOLOGY

A retrospective case control study was conducted in Hospital Universiti Sains Malaysia, Kubang Kerian from May 2012 till November 2015. Patients who had HRCT scan of the temporal bone in Department of Radiology from 1st May 2009 till 30th August 2015 were searched from GE Centricity Picture & Archiving System (PACS), and medical record of these patients were reviewed.

All patients (6 months old or above) who were diagnosed to have unilateral or bilateral SNHL by otorhinolaryngologist and had bone-conduction and air-conduction thresholds within 10 dB of each other, and thresholds are higher than 25 dB on pure-tone audiometry (PTA) examination were selected as study sample. Patients referred for temporal HRCT due to reasons other than conditions involving inner air such as unilateral cholestatoma, infection or trauma were included for control group. Since these conditions are mostly manifest unilaterally, the contralateral ear with normal hearing condition confirmed by careful review of medical record (including PTA) were taken. Patients with abnormal or suspicious involvement of inner ear structures in normal side of ear detected after reviewing HRCT images were excluded.

Patient's ear with gross structural inner ear abnormality, disease involving inner ear structures/temporal bone such as tumors or infection, deformity of the temporal bone or skull and involved with traumatic fracture of temporal bone detected on HRCT, had previous operation of temporal bone and poor quality of images that hinder for interpretation (due to motion, metal or others artifacts) were also excluded. Ethical approval was obtained from Human Research Ethics Committee, USM, including a permission to review medical record and retrieve CT images for analysis.

All scans were performed on 128-slice Siemens Somatom Definition CT scanner. The imaging protocol were used for HRCT temporal bone with zero gantry angle, 120 kV and effective 230 mAs, slice thickness of 0.4 mm, pitch of 0.85, field of view (FOV) of 189 mm and with a high-resolution bone algorithm covering whole petrous pyramid bone. All the images were reformatted to bone window (Kernel H70h Syngo, Siemens) at CT console and then were sent to PACS storage.

CT Images of temporal bone were analyzed using GE PACS Universal Viewer (version 6) on diagnostic workstation with 2-Megapixel 21-inches greyscale monitor. The measurement of the vestibular width, cochlear basal turn width and lateral semicircular canal bony island width were made using a computer-based caliper on a 512 x 512-pixel image and zoom factor of 2.3 under a window level of 700 HU and a window width of 4,000 HU. This is the best conditions showing low attenuation of inner ear structures.

Three identifiable inner ear structures were measured in designated slice on axial plane (Fig 3)**.** A modified methods were used for measurement of this structured that is simple, repeatable and comparable in different studies (Lan *et al.*,2009; Purcell *et al*., 2003b).

Cochlea was identified as a spiral tubular structure within temporal bone with soft tissue density within adjacent to the blind end of internal auditory canal. Its axis is vertically oriented with the base at below. On the CT scan images maximum cochlear basal turn width measured as a distance between its bone edges on axial plan among the slices displaying it at the line perpendicular to middle of its long axis (Fig. 3a and 3d).

Vestibule is a secular structures within temporal bone with soft tissue density within connected to the semicircular canals. Its maximum width measured as distance between two

bone edge among the slices displaying it in the middle of line perpendicular to its longitudinal axis (Fig. 3b and 3d). Lateral semicircular canal is one of three semicircular canals that located in axial plan, lateral to the vestibule. Maximum diameter of its bony island measured as the distance of two bone edge among the slices displaying it in the line perpendicular to long vestibular axis (Fig. 3c and 3d). The measurements were repeated three times and average of measurement was calculated. All data were entered into the SPSS data sheets.

Validation of these measurements were made by an independent experienced radiologist using thirty percent of randomly selected samples using Interclass correlation (ICC) (*Appendix*). Mean and Standard Deviation (SD) of were calculated for the vestibular width, cochlear basal turn width and lateral semicircular canal bony island width. Independent T-test statistical test was used to compare the mean width of determined inner ear structures and α will be taken at 5%.

RESULTS

Fifty ears with SNHL were taken in this study. The SNHL abnormalities were found in the 28 patients (22 patients with bilateral and 6 patients with unilateral disease). Structural abnormality was found in three patients with SNHL disease (bilaterally in 2 cases and unilateral in one case). These cases were excluded from the study due to absence or incomplete formation of vestibule or cochlea, where measurement was not possible. Finally, 45 ears with SNHL and 45 ears with normal inner ear structures and normal hearing (control group) were included in the study.

Twenty-five ears of patients with SNHL were male and 20 ears were from female, same as control group. The age of patients with SNHL ranged from 2 years to 23 years old with mean of 9.98 years old. The age range for control group was 2 to 76 years old with mean of 29.55 years old.

Table 4.1 shows the mean of cochlear width in SNHL and control groups. There was no significant difference in the mean width of cochlea scores between two groups (*P value* >0.05). Table 4.2 shows the mean vestibular width in SNHL and control groups. The results

showed no significant difference between the mean width of vestibule between SNHL and control groups (*P value* >0.05). Table 4.3 shows the mean width of semicircular canal bony island in SNHL and control groups. The result shows no significant differences in mean semicircular canal bony island width between two groups (*P value* >0.05).

DISCUSSION

SNHL include a wide range of abnormalities along a pathway extending from the sensory receptors of the inner ear to the cortical processing centers of the brain. These cases were inferred to arise largely as developmental, structural, or functional abnormalities within the inner ear. However, the primary site of damage cannot be identified from clinical characterization of the hearing loss.

Based on current understandings, identification of morphogenetic malformations such as Mondini deformity and Michel aplasia are not difficult. However, less severe dysplasia may not be obvious in the current acquired HRCT images or missed by simple visual inspection of the radiological images (Purcell *et al*., 2003b). Recognition of these less severe dysplasia are strongly dependent on the experience of the clinicians. Providing a standardized normal measurement could be helpful in detecting these abnormalities.

Based on current literature available, measurements of inner ear bony structures in SNHL patients and normal subjects, and its reproducibility are still equivocal. There are only few studies which were conducted to assess the size of inner ear structures, but each study uses their own method for measurement in different part of inner ear's structures and in different planes. The comparisons between previous studies are impossible because of the differences in methods of measurements used. In current study, the most suspicious part of inner ear bony structures at the most accessible plane (axial CT scan without 3D reconstruction) were used for measurements. A precise method for measurement also was designed that can be repeated and comparable with the future studies (Fig 3)**.**

The inner ear bony structures (vestibule, cochlea, semicircular canals) reach the adult size 6 months after birth (Jackler *et al*., 1987). No more increasing in size noted after this age (Elias *et al.*, 1998) (Pelliccia *et al*., 2014). It means that there is no significant difference in size of

this structures at infant after 6 months till old age, so the age was not influence the measurements in our study.

In this study, patients with grossly abnormal HRCT were excluded. Morphologic finding of inner ear structures were grossly abnormal in 10% of ears with congenital SNHL disease. These abnormalities were categorized as unilateral incomplete partition type II (classic Mondini deformity) in one patient, bilateral incomplete partition type I in another patient and bilateral Michel deformity in the last case (Figure 4)**.** Majority of SNHL patients in this study is caused by abnormal sensory epithelium of membranous labyrinth.

Results showed no significant difference in all three measurements between SNHL patients and healthy individuals which is in agreement with a study conducted by Chen *et al*., 2008. He evaluated total of 204 patients (408 ears) which included 188 ears with SNHL and 220 ears without SNHL underwent temporal bone CT scans or magnetic resonance imaging (MRI) as part of their routine radiologic evaluation for diagnoses including normal hearing with otologic symptoms, conductive hearing loss (CHL), and SNHL between 2001 and 2004. Their results demonstrated no statistically significant differences between inner ear measurements in those with SNHL and control group (Chen *et al*., 2008). They conclude that the inner ear measurements also did not appear to reliably differentiate between SNHL and non SNHL ears. This measurements only may help in identifying vestibulocochlear dysplasia that otherwise may be missed and thus should be considered to complement visual analysis of temporal CT scans (Chen *et al*., 2008).

In contrary, Lan *et al.* (2009), retrospectively reviewed the high-resolution CT scans of 45 ears in 27 patients with congenital SNHL and normal radiological images and 45 ears in 41 patients with normal inner ear structures and normal hearing. They found that bony island width of the superior semicircular canal, bony island width of the lateral semicircular canal and maximal height of cochlea in SNHL group are significantly larger than control group. They also found that there were no significant differences between two groups in the measurements of the lumen width of superior semicircular canal (SSCC), lateral semicircular canal (LSCC) and posterior semicircular canal (PSCC), length of inferior limb of PSCC, maximal length of cochlea, and maximal width and length of vestibule. They also concluded that standardized measurements of bony labyrinth of inner ear on temporal bone CT can identify subtle abnormalities of inner ear in patients with congenital SNHL having grossly

normal radiological images. In their study, ten different variables within inner ear structure were assessed. However, there is no clear description of the measured area given in their methodology which might create some inconsistency. In this current study, LSCC bone island width was measured in its maximum width in a line perpendicular to vestibular axis which is not defined specifically in their work.

In another study by Yamashita *et al*. (2011), retrospectively reviewed the HRCT images of the temporal bone obtained from consecutive patients to determine whether there is a correlation between the size of LSCC bony island width and SNHL. A total 136 ears of 68 patients were included in this study. They compared hearing levels among the patient group with normal-sized, small and very small LSCC as defined by the width and cross-sectional area of the bony island using one-way ANOVA. They found no significant correlation between LSCC bony island width and hearing level. No significant difference in hearing levels was also found among groups of the normal-sized, small and very small LSCC. They concluded that there is no correlation between isolated small LSCC Bone island and SNHL.

In contrast with this current study, Purcell *et al*. (2003), measured the cochlea, vestibule, and semicircular canals (SCCs) on axial and coronal temporal bone CT scans among 15 patients with normal hearing and 15 patients with congenital SNHL and grossly normal temporal bone CT scans. They reported significant differences in the measurements of the cochlea and SCCs between patients with and without SNHL. On axial section, the lumen of the cochlea's basal turn in samples from the SNHL group was smaller (mean 1.96 mm with SD 0.11mm) than in control group (mean 2.15 with SD 0.18) and SSCC bony width in the SNHL patients was larger than in the control group (mean 5.17 mm with SD 0.42 mm vs. mean 4.89 with SD 0.45). This was also true for LSCC bony width. On coronal section, the lateral SCC bony width in the SNHL group again proved to be larger than in the control group (mean 3.71 mm with SD 0.37 mm vs. mean 3.45mm with SD 0.42). The study reported that inner ear measurements on temporal bone CT scan of patients with congenital SNHL and radiologically undetectable abnormalities have identified subtle bony abnormalities of the cochlea and SCC.

Purcell *et al*. (2003), also conducted another study. They tried to standardize the measurements of inner ear structures on temporal bone CT scan. Study concluded that the vertical height of the cochlea on coronal scan and the size of the central bony island within

the LSCC on axial scan are useful measurements to diagnose common inner ear malformations (Purcell *et al.*, 2003b). The difference between results of Purcell studies compared with this current study might be explained by different in study design (different plane of CT scanning and different method of measurement). Limited number of samples used in both of his studies also might adversely affect final results.

In 2006, Purcell performed another study to assess the reproducibility of measurements of the cochlea and LSCC. He tried to determine if abnormal measurements can predict SNHL. Study independently measured the cochlear height on coronal section and the LSCC bony island width on axial section on 109 temporal bone computed tomography scans. Cochlear height of less than 4.35 mm was considered indicative of cochlear hypoplasia. LSCC bony island less than 2.59 mm was defined as hypoplastic and LSCC bony island greater than 4.79 mm was defined as hyperplastic. They found that cochlear hypoplasia (<4.4 mm) had a positive predictive value of 100% for SNHL, whereas cochlear hyperplasia and bony island dysplasia were less predictive. They suggested that measurements of coronal cochlear height and axial LSCC bony width have a reproducibility and can identify bony labyrinth abnormalities missed by visual inspection alone. They recommended using these three measurements on every temporal bone CT to identify most commonly encountered abnormalities of the bony labyrinth among SNHL patients. They also suggested that interpretation of the temporal bone CT can be greatly enhanced by the use of three standardized measurements: cochlear height, bony island of LSCC, and dimension of the vestibular aqueduct (Purcell *et al.*, 2006).

The results Purcell *et al* study, 2006 is in contrast with our current study because in our study. This might be explained the fact that mentioned study did not separate SNHL patients with grossly normal bony labyrinth from the patient with apparently abnormal inner ear structures. This can in turn, make bias in mean measurement of the SNHL patient with subtle or no bone abnormality. Different method of measurements also may affect the results.

CONCLUSION

This current study measured vestibular, cochlear and lateral semicircular bony island width among SNHL patients were compared with control group. Obtained results revealed no significant correlation between cochlear, vestibular and lateral semicircular bone island width among SNHL patients in comparison with normal hearing population.

The results are in agreement with the belief that developmental malformations limited to the membranous labyrinth is not associated with malformation in bony labyrinth. Consequently, these measurements do not have reproducibility in predicting SNHL in the grossly normal inner ear structures.

Since there is still no standardized method of measurement of the size of inner ear structures, careful methodology especially precise definition of measured area must be standardized to assist comparison between studies.

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TABLES AN FIGURES

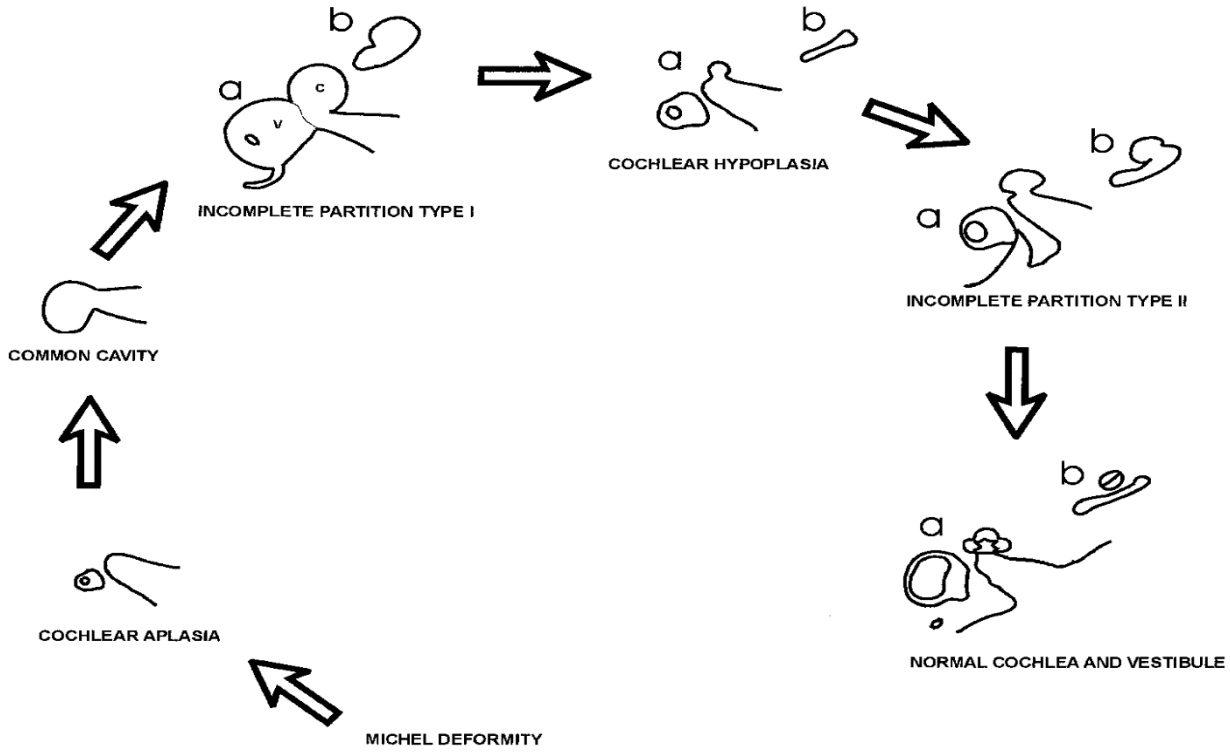

Figure 1: Schematic representation of different stages of developmental arrest in the inner ear development. The letters a and b represent sections through the internal auditory canal and round window respectively. (Jackler *et al*., 1987).