

**MASTERS DEGREE IN
COMMUNICATION PATHOLOGY 2013**
An Auditory Profile of Sclerosteosis

In fulfilment of the requirements for the degree of M. Communication Pathology
in the Department of Communication Pathology,
Faculty of Humanities, University of Pretoria, South Africa.

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DECLARATION

Name and student number: Jenni-Mari Potgieter

Assignment topic/ report: An audiological profile and database of patients with sclerosteosis: A longitudinal study

I declare that this assignment/report is my own original work. Where secondary material has been used (either from a printed source, a previous report or the internet), this has been carefully acknowledged and referenced. I understand what plagiarism is and am aware of the department's policy in this regard.

Signature: 

Date: 6 June 2013

With due acknowledgement to the Department of English at the University of Pretoria

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ABBREVIATIONS

ABR:	Auditory Brainstem Response
ABG:	Air Bone Gap
BAHA:	Bone Anchored Hearing Aid
CT:	Computed Tomography
DPOAE:	Distortion Product Otoacoustic Emission
ECV:	Ear Canal Volume
OI:	Osteogenesis Imperfecta
PTA:	Pure Tone Average
SRS:	Speech Recognition Score
SRT:	Speech Reception Threshold

ABSTRACT

Sclerosteosis is a rare genetic bone dysplasia disorder characterised by generalised craniotubular bone modelling. Alongside many clinical appearances marked in sclerosteosis, the auditory system is considerably compromised on several levels during the disease progression. Extensive otolaryngological research on the history of sclerosteosis, the clinical presentation of sclerosteosis, radiographic studies and the gene causing the condition had been documented. No studies had been found describing the audiological profiles, auditory functioning and abnormalities for subjects with sclerosteosis. Thus the object of this study aimed to describe the auditory profile of subjects with sclerosteosis.

A cross-sectional descriptive research design and quantitative research approach was followed to investigate the auditory characteristics of subjects with sclerosteosis. Subjects were selected from a database of patients with confirmed diagnoses of sclerosteosis. Ten subjects responded and provided written informed consent. Test procedures included otoscopy, tympanometry, acoustic reflexes, diagnostic pure-tone air- and bone-conduction audiometry, speech audiometry, distortion product otoacoustic emissions (DPOAE), auditory brainstem responses (ABR) and computed tomographic (CT) scans. The subjects were assessed with a comprehensive audiological test-battery within a single test session lasting approximately two hours. A CT scan was conducted on a separate occasion shortly after the audiological data were obtained.

Normal type A tympanograms were obtained in 50% (n=10/20) of ears. All subjects presented with mixed hearing losses varying from moderate (5%; n=1), severe (55%; n=11) and profound (40%; n=8) degrees across ears. Hearing loss configurations ranged from rising (15%), sloping (35%) and air-conduction thresholds peaking at 2000 Hz (50%). Air bone gaps (ABG) were larger in older subjects, although not statistically significant ($p>.05$). The CT scans indicated anatomical abnormalities of the external auditory canal, tympanic membrane, middle ear space, ossicles, oval window, round window and the internal auditory canal.

The progressive abnormal bone formation in sclerosteosis involved the middle ear, the round and oval windows of the cochlea and internal auditory canal. The progressive

abnormal bony overgrowth, which is the hallmark of sclerosteosis, led to functional impairment at various levels in the auditory system. The current findings provided a comprehensive auditory profile for sclerosteosis. Results might be utilised alongside future research findings to direct criteria and audiological indications for surgical and audiological intervention.

Keywords: Bone dysplasia, conductive hearing loss, sclerosteosis, sensorineural hearing loss.

1. INTRODUCTION

1.1. Background

Sclerosteosis and Van Buchem disease are both rare genetic sclerosing bone dysplasia disorders characterised by generalised craniotubular bone modelling (Hamersma & Hofmeyr, 2007; Moester, Papapoulos, Löwik, Van Booijen, 2010; Stein *et al.*, 1983). These two disorders were first described in the 1950s as different clinical entities with closely associated phenotypes (Moester *et al.*, 2010; Van Buchem, Hadders, Ubbens, 1955). The auditory system in sclerosteosis was significantly compromised on several levels during the course of the disease progression, along with many other clinical presentations (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004).

Sclerosteosis is a benign form of excessive bone formation. Among the Afrikaners of South Africa of Dutch, French and German descent, 74 cases had been identified (Hamersma & Hofmeyr, 2007). Sclerosteosis is inherited in an autosomal recessive manner (Beighton, Hamersma & Brunkow, 2007). There is a 25% probability for each sibling in a proband to be affected, 50% probability to be an asymptomatic carrier and a 25% probability to be unaffected (Beighton *et al.*, 2007). The prevalence of sclerosteosis in the Afrikaner community in South Africa was estimated at 1 to 60 000 (Beighton & Hamersma, 1979).

Van Buchem disease is also an inherited sclerosing bone dysplasia that belongs to a collective term, craniotubular hyperosteosis (Beighton, Barnard, Hamersma, Van der Wouden, 1984; Breighton, Horan, Hamersma, 1977). Craniotubular hyperosteosis is defined as a skeletal deformity that results from bony overgrowth (Breighton *et al.*, 1977). Van Buchem disease has an autosomal recessive inheritance, but autosomal dominant cases with endosteal hyperostosis had also been reported (Cook, Phelps, Chandy, 1989).

Additional cases of sclerosteosis and Van Buchem disease had been described in different parts of the world, with an increased incidence in the Afrikaner population of South Africa (Cook *et al.*, 1989). Cases had been reported in Spain, Brazil, the United States of America, Germany, Japan, Switzerland and Senegal (Hamersma, Gardner, Beighton, 2003; Kim *et al.*, 2008; Moester *et al.*, 2010).

1.2. Etiology

A study in Belgium identified loss of function mutations in the SOST (two-exon) gene as a reason for sclerosteosis (Balemans & Van Hul, 2004). The localisation of the SOST gene is mostly restricted to the area where osteogenesis takes place (Balemans & Van Hul, 2004). Sclerostin is abundantly present in osteocytes and osteocytic canaliculi within bone (Balemans & Van Hul, 2004). Osteocytes secrete sclerostin controlling proliferation and differentiation of osteoblastic cells and the activity of mature osteoblasts (Balemans & Van Hul, 2004; Leupin *et al.*, 2007).

Recent studies discovered that excessive bone formation was caused by defective activity of the sclerostin protein, which was a product of the SOST gene in chromosome 17q12-q21 (Hamersma & Hofmeyr, 2007; Moester *et al.*, 2010). In sclerosteosis, five mutations had been identified. Three of these mutations introduced a premature termination codon and the other two mutations interfered with the joining of the gene (the splice site mutation being IVS1+3 A→T) in sclerosteosis (Balemans *et al.*, 2002; Moester *et al.*, 2010). No mutations within this gene were present in Van Buchem disease. Instead 35 kb downstream of the SOST gene a 52 kb deletion had been identified (Moester *et al.*, 2010). This deletion contained managing elements for SOST transcription, having the ability to produce a phenotype closely approximating sclerosteosis (Moester *et al.*, 2010).

1.3. Clinical Features

Sclerosteosis and Van Buchem disease shared similar clinical manifestations. Both disorders were progressive. Prognosis in Van Buchem disease was relatively benign, but in sclerosteosis prognosis can potentially be lethal (Beighton *et al.*, 2007). Individuals with sclerosteosis suffered from intracranial pressure being one of the reasons why prognosis could be lethal. Several affected adults had died suddenly from impaction of the brainstem in the foramen magnum. The elevations in intracranial pressure caused the individuals with sclerosteosis to suffer from severe headaches, whilst individuals with Van Buchem disease had normal intracranial pressure (Beighton *et al.*, 1984).

As these two disorders progressed, overgrowth of the mandible and brow became evident. Teeth remained unaffected in Van Buchem disease, but in sclerosteosis teeth

presented irregular and malocclusion had been noted (Beighton *et al.*, 1984; Beighton *et al.*, 2007; Beighton *et al.*, 1977).

Individuals with Van Buchem disease usually had normal stature, while those with sclerosteosis were marked by gigantism (Beighton *et al.*, 1984; Beighton *et al.*, 2007; Beighton *et al.*, 1977). Gigantism refers to an individual's tall stature during mid-childhood, their increased head circumference and excessive weight due to bony overgrowth (Hamersma, *et al.*, 2003). Van Buchem disease presented with moderate cranial hyperostosis. Mild distortion of tubular bones of the hands and feet were noticed. Gross cranial hyperostosis and marked distortion of tubular bones of hands and feet were evident to sclerosteosis (Beighton *et al.*, 1984; Beighton *et al.*, 2007; Beighton *et al.*, 1977).

Facial nerve palsy is a common feature in both disorders caused by cranial nerve entrapment (Beighton *et al.*, 1984; Beighton *et al.*, 2007; Beighton *et al.*, 1977). The progressive bone formation caused compression of the 7th cranial nerve in the bony foramina (Hamersma *et al.*, 2003). The entrapment of the 7th cranial nerve could lead to acute recurrent attacks of facial palsy or weakness (Hamersma, *et al.*, 2003). The first attack of facial nerve palsy in sclerosteosis could occur during infancy or at birth (Breighton & Hamersma, 1979). The facial nerve palsy usually recovers partially after 3 to 4 months, but by mid-childhood permanent bilateral facial weakness occurs (Breighton & Hamersma, 1979).

Hearing loss and deafness were evident in both disorders (Beighton *et al.*, 1984; Beighton *et al.*, 2007; Beighton *et al.*, 1977). Bony overgrowth in the middle ear caused a conductive hearing loss during the early stages of sclerosteosis (Breighton & Hamersma, 1979; Hamersma *et al.*, 2003). The conductive hearing loss was mainly caused by impairment of movement of the middle ear ossicles (Breighton & Hamersma, 1979; Hamersma *et al.*, 2003). A sensorineural component later developed which might result from closure of the round and the oval windows of the cochlea and compression of the 8th cranial nerve in the internal auditory canals (Breighton & Hamersma, 1979; Hamersma *et al.*, 2003).

Syndactyly is a characteristic feature that distinguishes sclerosteosis from Van Buchem disease. The presence of syndactyly aids in the early identification of sclerosteosis during the neonatal period (Brighton & Hamersma, 1979). The severity of syndactyly varied as it ranged from minor skin webbing to complete bony union (Brighton & Hamersma, 1979; Hamersma *et al.*, 2003). The individual's toes usually remained unaffected, but the nails might be dysplastic especially on the great toes (Brighton & Hamersma, 1979; Hamersma *et al.*, 2003).

1.4. Management

The symptoms and complications of excessive bony overgrowth are currently managed by surgical treatment (Hofmeyr & Hamersma, 2004). Proptosis was managed by orbital decompression (Hofmeyr & Hamersma, 2004). Postoperative blindness had however been encountered in several cases after orbital decompression (Hofmeyr & Hamersma, 2004).

Medullary coning was the source of intercranial pressure in sclerosteosis. The intercranial pressure resulted in herniation of the cerebellar tonsils through the foramen magnum, compressing the medulla causing sudden death (Du Plessis, 1993; Hofmeyr & Hamersma, 2004). To prevent death, an emergency posterior fossa craniectomy should be conducted to decompress the brain (Du Plessis, 1993; Hofmeyr & Hamersma, 2004). Follow-up craniectomies of the frontal and parietal skull bones were done, as well as widening of the foramen magnum (Du Plessis, 1993; Hofmeyr & Hamersma, 2004). Other cosmetic surgeries were done on the mandible, syndactyly, and skeletal deformities for functional purposes (Hofmeyr & Hamersma, 2004).

One of the most significant challenges was the management of hearing loss, which had limited success (Hofmeyr & Hamersma, 2004). The encroachment of the dense bone on the round and oval windows needed to be drilled away, which might cause sensorineural damage to the high frequencies of hearing (Hofmeyr & Hamersma, 2004). Decompression of the 8th cranial nerve had been done previously due to bony dysplasia. This procedure might however cause damage to the nerve, contributing to sensorineural hearing damage (Hamersma & Hofmeyr, 2007). Recurrent release of the ossicles temporarily improved hearing, but progressively bone fixated the ossicles again (Hofmeyr & Hamersma, 2004). The size of the annulus of the windows stayed the same because

the bony overgrowth only affected the outer surface of the otic capsule (Hofmeyr & Hamersma, 2004). Patients with sclerosteosis and Van Buchem disease usually ended up wearing a hearing aid, due to the complications of the external ear canal, middle ear and inner ear. Successful fitting of bone anchored hearing aids (BAHA) had been documented in Van Buchem disease, but no documentation existed on the success of hearing aid fittings and BAHAs in sclerosteosis (Hofmeyr & Hamersma, 2004).

The vestibular system might also be affected, causing dizziness, necessitating decompression of the vestibular nerve (Hofmeyr & Hamersma, 2004). Facial nerve decompression might also become necessary with a patient that presented with facial nerve palsy (Hofmeyr & Hamersma, 2004). When the facial pain was severe, decompression of the trigeminal nerve had been reported to alleviate the discomfort (Hofmeyr & Hamersma, 2004).

1.5. Problem statement

Even though sclerosteosis is a rare condition, and mostly restricted to the Afrikaners of Dutch, French and German descent, it had also been identified in other parts of the world (Hamersma *et al.*, 2003; Kim *et al.*, 2008; Moester *et al.*, 2010). This rare condition with its clearly delineated symptoms and progression, increasing hearing loss, bony growth that potentially affected the outer ear, middle ear, cochlea and auditory nerve posed a significant challenge related to communication. The exact auditory profile and outcomes were however still unclear.

A literature review indicated that there had been extensive otolaryngological research on the history of sclerosteosis, the clinical presentation of sclerosteosis, radiographic studies and the gene causing the condition (Balesman, Cleiren, Siebers, Horst, Van Hul, 2005; Beighton, Cremin & Hamersma, 1976; Beighton *et al.*, 1983; Beighton *et al.*, 2007; Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004; Stein *et al.*, 1983). No studies had however been found on audiological profiles describing the auditory functioning and abnormalities for individuals with sclerosteosis. Hofmeyer and Hamersma (2004) indicated that there was a dearth of research with regard to nonsurgical management of sclerosteosis. As a result it was important to describe the auditory functioning of sclerosteosis according to an audiological test-battery and view the abnormalities through CT scans. The CT scans would provide valuable information

on the auditory structures affected by the disease and the audiological tests would indicate how these abnormalities affected the auditory functioning of sclerosteosis. This investigation would aid in gaining a better understanding of the involvement of hearing and auditory functioning in these subjects, but might also assist in directing nonsurgical and surgical management decisions. Thus, this study aimed to describe the auditory profile of subjects with sclerosteosis.

2. METHODOLOGY

2.1. Research Aim

To determine and describe the auditory profile (audiological and radiological) of patients with sclerosteosis.

The secondary research objectives subsequently identified were:

Sub-aim 1

To describe the audiological findings for subjects with sclerosteosis.

Sub-aim 2

To describe radiological findings of the auditory system for subjects with sclerosteosis.

Sub-aim 3

To compare the audiological and radiological findings in subjects with sclerosteosis.

The results of sub-aim 1, 2 and 3 were compiled and described in the article titled “An Auditory Profile of Sclerostosis” (Chapter 3) and accepted for publication in the *Journal of Laryngology and Otology*, 21 April 2013.

2.2. Research design

A descriptive group and multiple single-subject research design were selected to investigate the auditory characteristics of subjects with sclerosteosis. It focused on providing an accurate, calculated description of the auditory, audiological and radiological aspects in each subject. The aim of the research was to present a profile of the audiological and radiological characteristics of each case and as a group (Struwig & Stead, 2001). The research also included a cross-sectional component, as the study was aimed at special data collection for the specific population of sclerosteosis, at a defined period of time (Babbie, 1973; De Vos, Strydom, Fouché, Delport, 2011). The research had been conducted to provide baseline information for later intervention studies.

A quantitative research approach was chosen for this study, since numerical data and statistical procedures were used to analyse and draw conclusion from the recordings

(Leedy & Ormrod, 2005). Data collection included tympanometry, pure-tone air- and bone-conduction audiometry, speech audiometry, OAEs, ABRs and CT scans.

2.3. Ethical Considerations

Research is an ethical enterprise and it follows a system of morals and rules for behaviour. Research ethics provide researchers with a code of moral guidelines on how to conduct research in an acceptable way (Struwig & Stead, 2001). The following ethical principles were adhered to in conducting this research project.

2.3.1. Ethical clearance

The study commenced after ethical clearance had been granted by the Faculty of Humanities Research Proposal and Ethics Committee of the University of Pretoria (Appendix A).

2.3.2. Beneficence and non-maleficance

The researcher had an ethical responsibility to protect the subjects with sclerosteosis within all probable realistic limits from any form of anxiety and discomfort that might arise from the research study (De Vos *et al.*, 2011). The researcher did not expose the subjects to any physical or psychological discomfort at any time, as the subjects were well-informed on the procedures and tests (Leedy & Ormrod 2001; De Vos *et al.*, 2011).

The welfare of the subjects with sclerosteosis was paramount in this study. The research involved non-invasive audiometric testing which included an otoscopic examination, tympanometry, pure tone and bone conduction audiometry, speech audiometry, DPOAEs and ABR testing, thus no harm was inflicted.

CT scans were conducted on nine subjects. The Radiology Department at Muelmed Mediclinic and relevant professionals adhered to the ethical issues regarding radiation. The subjects were dressed in lead attire to prevent radiation of the entire body. Only scans of the brain were conducted. The procedure lasted less than 10 minutes, thus no harm was inflicted.

2.3.3. Informed consent

Each participant received a letter of informed consent before testing commenced (Appendix B). The letter described the nature of the components of the study, and the terms and conditions for participation. Confidentiality was maintained by assigning a code to each subject. The letter also stated that participation was voluntary, and that subjects could withdraw from the study at any time. Contact details of the researcher and study supervisor were provided whenever the subjects had any questions. Subjects had to sign the letter of informed consent before testing could begin.

Prof. L.M. Hofmeyr and Prof. H. Hamersma were provided with a letter to request permission to review subject information as well as accessing subjects' contact details (Appendix C). Prof. L.M. Hofmeyr gave written permission and Prof. H. Hamersma provided verbal permission to access subject information and contact details for the research study (Appendix C).

A letter was submitted to the Radiology Department at Muelmed Mediclinic requesting permission to conduct the radiographic tests on the subjects. The letter also informed the Department on the nature and potential benefit of the study (Appendix D). Permission to conduct radiographic tests was given by Dr. A.A.S. Burger at the Radiology Department at Muelmed Mediclinic (Appendix D).

2.3.4. Deception of subjects

Research was not misrepresented and all findings were reported in a complete and honest manner (Leedy & Ormrod, 2001). All the subjects were provided with a letter explaining all the testing procedures to ensure that the researcher did not mislead the subjects (De Vos *et al.*, 2011). No information had been withheld or incorrect information had been offered to confirm the participation of subjects (De Vos *et al.*, 2011). All research findings were made available to the subjects and doctors on request. The beliefs and values of the subjects were respected at all times (Leedy & Ormrod, 2001).

2.3.5. Violation of privacy

Every subject had the right to privacy and the decision to what range his or her behaviour, attitudes, beliefs and test results would be exposed. It was the duty of the researcher to respect the privacy of the subjects and to act with understanding where

privacy of subjects was pertinent (De Vos *et al.*, 2011). The research study respected the privacy of file information of the subjects at all times (Leedy & Ormrod, 2001). By no means had any audiological, clinical and radiographic results been presented in such a way that others became aware of the subject's test results, unless the subject had granted permission for disclosure (Leedy & Ormrod, 2001). Confidentiality of subject information was maintained. No names had been used when describing the subjects and codes had been assigned to each subject in the research report.

2.3.6. Actions and competence of researcher

The researcher was ethically obliged to be competent, honest and skilled to conduct the various audiometric testing (De Vos *et al.*, 2011). The researcher ensured to be competent due to her qualification as an Audiologist. Two research supervisors and an Otolaryngologist were also involved in the research. They assisted to ensure a seamless research process. All the professionals involved in the study were registered with the Health Professions Council of South Africa.

The research had been conducted professionally. Firstly, a pilot study had been carried out to determine whether the test material were sufficient to describe the subjects' hearing and if the data being collected would be comprehensive. The audiometric tests that had been used in the study were objective and subjective, and all findings had been carefully analysed and recorded. The CT scans were objective in nature, and Dr. A.A.S. Burger (Radiologist) and Prof. L.M. Hofmeyr (Otolaryngologist) carefully analysed the results.

2.3.7. Dissemination of findings

A research report had been made available to the scientific community, subjects and the hospital where the research was conducted (Struwig & Stead, 2001). The report contained all the information necessary for the readers to understand what had been investigated and the outcomes of the investigation (De Vos *et al.*, 2011). The subjects had been informed that the research might be published as a journal article, discussed at conferences, seminar presentations, and academic gatherings which adhere to ethical considerations. The findings were revealed to the subjects as a form of recognition for their participation in the study and in a manner to maintain a good relationship with the subjects for future research in sclerosteosis (De Vos *et al.*, 2011).

2.3.8. Reliability and Validity

Struwig & Stead (2001) stated that reliability referred to the accuracy, consistency and stability of test scores to replicate the measurements. Validity referred to the appropriate and dependable conclusions deducted from the research (Struwig & Stead, 2001). The reliability and validity of the data collected were ensured by the following.

- Objective and subjective test measures were used during data collection. The test measures ensured accuracy of results, as correlation between the test measures was observed.
- Test results were accurately interpreted and scored as the research audiologist, research supervisor, otolaryngologist and radiologist aided in analysing the measurements.
- The audiometric tests were administered correctly, adhering to the standards set forth by the University of Pretoria, Department of Communication Pathology.

2.3.9. Acknowledgement

Plagiarism was avoided by acknowledging all professionals who contributed to an integral part of this research project. All literature references were also cited in the research report (Struwig & Stead, 2001).

2.4. Research Subjects

2.4.1 Sampling procedure

Purposive sampling was used to select subjects for this study. Purposive sampling was primarily used when there were a limited number of people in the area being researched, and depended on the appropriateness of the population. It was typically used to illustrate the characteristics of interest (De Vos *et al.*, 2011).

Purposive sampling was implemented because the sample population studied were rare and difficult to locate, as there were only 36 subjects with diagnosed sclerosteosis alive in South Africa at the time of data collection. Prof. H. Hamersma and Prof. L.M. Hofmeyr had well-established connections with subjects diagnosed with sclerosteosis. Most of the subjects were diagnosed by Prof. H. Hamersma, who had a lifelong interest in

rehabilitating sclerosteosis. Prof. H. Hamersma and Prof. L.M. Hofmeyr gave permission to access the sclerosteosis database which contained the contact information of 18 subjects.

It was of critical concern that the sample population had properties and characteristics which represented that of sclerosteosis to allow accurate generalisation (Bless, Higson-Smith, Kagee, 2006). Therefore the inclusion criteria were as follow:

- A heterogeneous population were studied, due to the rarity of the disorder.
- Subjects of all ages were included.
- The subjects who agreed to participate in the research study had to have a confirmed diagnosis of sclerosteosis. The subjects were confirmed and diagnosed by Prof. H. Hamersma (Otolaryngologist).
- The subjects had to undergo a diagnostic audiological evaluation which included an otoscopic evaluation, acoustic immittance measures, pure-tone air- and bone-conduction audiometry, speech audiometry, DPOAEs and ABRs.
- CT scans had to be conducted for each subject. The radiographic scans were conducted by the Radiology Department at Muelmed Mediclinic. Prof. L.M. Hofmeyr (Otolaryngologist) and Dr. A.A.S. Burger (Radiologist) analysed the radiographic scans to compare with the audiological findings.

2.4.2 Description of subjects

The researcher had access to 18 subjects who met the criteria specifications to participate in the research. They were contacted telephonically and invited to participate. Ten subjects responded and provided written informed consent. Two of the 18 subjects were very young (younger than five years of age). The parents of the young subjects gave consent to participate in the research study. Testing was attempted on one of the subjects. The testing procedures could not be completed. The remaining 4/18 subjects were not interested to partake in the research study. The research subjects were assessed with a comprehensive audiological test-battery within a single test session, lasting approximately two hours. Nine of the ten subjects underwent CT scans that lasted approximately 10 minutes. One of the subjects lived outside of the Gauteng region and experienced transportation difficulties, therefore was not able to attend his appointment

at the Radiology Department at Muelmed Mediclinic. Table 2.1 provides a basic description of the research subjects.

TABLE 2.1.
Description of the sclerosteosis subjects according to age, gender and race ($n=10$).

Subjects	Age	Gender	Race
1	72	Female	White
2	55	Female	White
3	20	Male	White
4	19	Female	White
5	45	Male	White
6	21	Female	White
7	14	Male	White
8	10	Male	White
9	40	Female	White
10	24	Female	White
Mean	32	60% Female 40% Male	White
Range	10-72	-	-

2.5. Material and Apparatus

The following test procedures were conducted after the subjects had signed the letter of informed consent. Test procedures included otoscopy, tympanometry, acoustic reflexes, diagnostic pure-tone air- and bone-conduction audiometry, speech audiometry, DPOAEs, ABR and CT scans.

2.5.1. Otoscopy and acoustic immittance measures

The otoscopic evaluation (ReddyLite™) was conducted in order to view any obstructive debris in the ear canals, which might be contra-indicative for other tests. The otoscopic examination indicated that all ears were free from any obstructive debris. Tympanometry (GSI Tymptstar, Grason-Stadler, Madison, WI, USA) was conducted bilaterally to measure static compliance, middle ear pressure and ear canal volume. The modified Jerger classification system for tympanometry (Jerger, 1970) was used to interpret the tympanogram type. Ipsi- and contra-lateral acoustic reflexes were measured using a 226 Hz probe tone frequency with pure tone octave stimuli from 500 to 2000 Hz for ipsi-lateral reflex recordings and 500 to 4000 Hz for contra-lateral reflex recordings. The stimulus was initially presented at 75 dB HL. The intensity was increased in 10 dB steps and

decreased in 5 dB steps until a reflex was elicited. A reflex threshold was the last visible deflection of 0.02 or more and was only accepted if it was repeatable.

2.5.2. Pure tone audiometry

A clinical audiometer (GSI 61, Grason-Stadler, Milford, NH, USA) was used to conduct pure tone air conduction, bone conduction and speech audiometry. All testing was conducted in a sound-treated booth using supra-aural earphones (Telephonics, TDH-49P) for air-conduction audiometry and a bone oscillator (Radioear, B-71) for bone-conduction audiometry. All hearing thresholds were measured in dB hearing level (dB HL). Octave frequencies between 250 to 8000 Hz were used for pure tone air-conduction audiometry, while the octave frequencies between 250 to 4000 Hz were utilised for bone-conduction audiometry. The pure-tone air- and bone-conduction threshold seeking procedures were carried out according to the modified Hughson-Westlake method (Hall & Mueller, 1997). The classification of hearing impairment severity and the audiometric configuration were classified according to the criteria provided by Jerger (Hall & Mueller, 1997).

2.5.3. Speech audiometry

Speech reception thresholds (SRT) and speech recognition monaural performance scores (SRS) were presented with live voice in Afrikaans, as all the subjects were Afrikaans speaking. The *Afrikaanse Spondee Woordelys* (Laubscher & Tesner, 1966) was used to obtain SRT. A list of six spondee words were presented until a subject detected 50% of the words correctly. The agreement between the pure tone average (PTA) and SRT should agree with +/- 7 dB in order to be reliable (Hall & Mueller, 1997). The *Afrikaans Foneties Gebalanseerde Woordelys* (Laubscher & Tesner, 1966) was used to obtain SRS across intensities. A list of twenty-five phonetically balanced word discrimination words were presented at three different intensities in order to obtain a percentage of words detected correctly for SRS. The SRS percentages were determined by initially presenting the phonetically balanced discrimination words 20 dB above the SRT of the test ear. The intensity was increased or decreased in 10 dB steps to obtain three different intensity scores. The SRS scores varied for all subjects depending on the degree of hearing loss.

2.5.4. Distortion Product Otoacoustic Emissions

DPOAEs were measured using an insert probe (Navigator Pro system, Biologic Systems Corp.). Two pure tones with a 1.22 frequency ratio (f_2/f_1) were used at non-equal sound pressure levels ($L_1=65$ dB SPL, $L_2=55$ dB SPL). The DPOAE amplitude was measured at the frequencies $2f_1-f_2$ with f_2 varying from 1008 to 8016 Hz (1008, 1266, 1570, 1992, 2508, 3164, 4008, 5063, 6352 and 8016 Hz). The average noise floor was approximated around the $2f_1-f_2$ frequency. The spectrum ranges for the upper frequency limits were 10k Hz and the decibel ranges at 100 dB. The DP-Gram analysis ranges maximized at 70 dB with a minimum level of -30 dB. The referencing data used were according to the Vanderbilt 65/55, 95 to 5th percentile norms. Data was interpreted according to these norms (Hall & Mueller, 1997).

2.5.5. Auditory Brainstem Response

The Navigator Pro system (Biologic Systems Corp) was also used to measure the ABR in each subject. The ABR was elicited using air-conduction click stimuli in a sound-treated booth. Following site skin preparation, three electrodes were placed with the non-inverting electrode on the high forehead (Cz), the inverting electrode on the test earlobe and the ground electrode on the contra-lateral earlobe. Impedance was kept <5 k Ω . Subjects were instructed to lie comfortably on a bed with their eyes closed. Rarefaction clicks were delivered monaurally through insert earphones. The stimulus rate was 11.1 stimuli/sec. Subjects were tested at an intensity of 90 dB nHL with a recording time window of 21 ms. The maximum amount of averaged recordings were 2000. The artifact rejection was set at 23.3 μ v and the recordings were filtered between 100 and 3000 Hz (Hall & Mueller, 1997; Hall & Swanepoel, 2010).

2.5.6. Computed Tomography Scans

CT scans were conducted on 9/10 subjects (one subject was not able to attend the appointment due to transportation difficulties) by the personnel of the Muelmed Mediclinic in Pretoria. The scans were all isometric voxels, supplied from 0.5 mm cross-sections with a shift of only 0.1 mm between adjacent sections. From these sections, axial and coronal reconstructions, as well as sometimes three-dimensional reconstructions were obtained. The lateral semi-circular canal was used as a reference for both the axial and coronal reconstructions. The irradiation per rotation measured at 200 mA and 500 mSec.

2.6. Data collection

2.6.1. Research Setting

The Department of Communication Pathology, University of Pretoria, was selected for conducting audiometric tests. The Department of Radiology, Muelmed Mediclinic, was selected to conduct CT scans. These departments were selected according to the following criteria:

- Department of Communication Pathology, University of Pretoria:
 - The Department of Communication Pathology was available for testing from Mondays – Fridays, 8:00 – 17:00.
 - The audiometric tests were conducted in a research facility.
 - All test equipment necessary to conduct the audiometric tests were available.
 - All test equipment received annual calibration and was in excellent working condition.
 - All tests were conducted in a quiet room.

- Department of Radiology, Muelmed Mediclinic:
 - The Department of Radiology was available to conduct CT scans from Mondays – Fridays, 8:00 – 17:00 and Saturdays, 8:00 – 13:00.
 - CT scans were conducted in a tertiary private hospital.
 - Dr. A.A.S. Burger had immediate access to the CT scans.
 - All the scans were stored on a database created for the subjects with sclerosteosis.

2.6.2. Data collection procedures

Data collection commenced after written informed consent had been obtained from each subject. Audiological data were collected in a once-off test session for each subject. A CT scan was conducted on a separate occasion, shortly after the audiological data were obtained. The data collection procedures were as follows:

- Prof. H. Hamersma and Prof. L.M. Hofmeyr were contacted to obtain permission to use the contact details of the subjects with sclerosteosis. Prof. L.M. Hofmeyr acted as one of the coordinators of the research study.
- Prof. L.M. Hofmeyr gave written consent to access subject contact details.
- Prof. H. Hamersma gave verbal consent to access subject contact details and provided the contact details of 18 subjects.
- The 18 subjects were contacted telephonically and informed on the motive for the research study, and the potential benefit and implications of the research study.
- Ten subjects gave verbal telephonic consent to participate in the research study.
- Data collection commenced in November 2010 and ended in January 2011. An additional subject was added to the research study in March 2012.
- Individual appointments were scheduled with each subject to commence testing at the Department of Communication Pathology, University of Pretoria.
- On arrival, each subject received a briefing of the test procedures and an information letter explaining each test and test procedure in detail.
- Each subject read through the information letter and provided written informed consent to partake in the research study.
- Before testing commenced, a short case history was conducted. The case history was not carried out as part of the data collection process, but merely for comprehensive purposes.
- A bilateral otoscopic examination was conducted, followed by tympanometry, pure-tone air- and bone-conduction audiometry, as well as speech audiometry. These results were recorded on an audiogram.
- Each subject was provided with a short break before starting with ABR and DPOAE testing.
- ABRs and DPOAEs were conducted and printed from a computer.
- The research audiologist scheduled and confirmed a CT scan appointment for each subject at the Department of Radiology, Muelmed Mediclinic.
- Each subject was welcomed at Muelmed Mediclinic by the personnel of the Department of Radiology. The subjects were informed on the procedures for the CT scan to follow.
- The radiology personnel applied the necessary ethical considerations for conducting CT scans.

- The CT scan data were analysed by Dr. A.A.S. Burger (Radiologist) and Prof. L.M. Hofmeyr (Otolaryngologist).
- Audiological test data were interpreted by three experienced clinicians.

2.6.3. Procedures for data processing and analysis

The research audiologist interpreted the raw data from the audiological tests separately and independently. The data were captured on Microsoft EXCEL 2003 spread sheets and the Statistic Package Social Sciences (SPSS) version 20 was used for statistical calculations and analysis.

- The non-parametric Independent Samples Mann-Whitney test was used to determine whether there was a difference between the ABGs found in older subjects compared to younger subjects.
- Mean values were used to analyse pure tone audiometry, ABGs, ABRs, SRS and SRT threshold data to determine the central tendency between the sections of data values.
- The standard deviations were calculated to determine the amount of variation that exists between the mean values in the various data sections.
- Minimum and maximum values were calculated to determine the best and the poorest ABGs, SRT, SRS and PTA thresholds found in sclerosteosis.

3. AN AUDITORY PROFILE OF SCLEROSTEOSIS

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3.1. Abstract

Objective: To characterise auditory involvement secondary to excessive craniotubular bone growth in subjects (n=10) with sclerosteosis.

Materials and methods: A cross-sectional, descriptive research design was followed with descriptive and comparative analyses.

Results and analysis: All subjects presented with bilateral mixed hearing losses from moderate (5%; n=1), severe (55%; n=11) to profound (40%; n=8) degrees across ears. Air bone gaps were larger in older subjects although not statistically significant ($p>.05$). Computed tomography scans indicated pervasive abnormalities of the external auditory canal, tympanic membrane, middle ear space, ossicles, oval window, round window, and internal auditory canal. Narrowed internal auditory canals corresponded to poor speech discrimination indicative of retro-cochlear pathology and absent auditory brainstem response waves.

Conclusion: Progressive abnormal bone formation in sclerosteosis involves the middle ear, the round and oval windows of the cochlea and internal auditory canal, compromising conductive, sensory and neural auditory pathways which result in moderate to profound mixed hearing losses.

Keywords: Bone dysplasia, conductive hearing loss, sclerosteosis, sensorineural hearing loss.

3.2. Introduction

Sclerosing bone dysplasias is a rare genetic disorder, characterized by generalised craniotubular bone modelling that results in an array of associated disorders, including auditory dysfunction (Hamersma & Hofmeyr, 2007; Stein *et al.*, 1983). Sclerosteosis is a benign form of excessive bone formation. Among the Dutch, French and German Afrikaner descendants of South Africa, 74 cases have been identified. (Hamersma & Hofmeyr, 2007). The inheritance pathway for sclerosteosis is autosomal recessive with a 25% probability for each sibling in a proband to be affected (Beighton *et al.*, 2007). There is also a 50% probability to be an asymptomatic carrier and a 25% probability to be unaffected (Beighton *et al.*, 2007). The prevalence of sclerosteosis in the Afrikaner community in South Africa has been estimated at 1 to 60 000 (Beighton & Hamersma, 1979).

Balemans and Van Hull explain loss-of-function mutations in the sclerostin/SOST (two-exon) gene as the cause of sclerosteosis (Balemans & Van Hul, 2004). The localisation of the SOST gene is mostly restricted to the area where osteogenesis takes place (Balemans *et al.*, 2005; Balemans & Van Hul, 2004). Sclerostin is abundantly present in osteocytes and osteocytic canaliculi within bone (Balemans *et al.*, 2005). Osteocytes secrete sclerostin controlling the proliferation and differentiation of osteoblastic cells and the activity of mature osteoblasts (Balemans *et al.*, 2005; Leupin *et al.*, 2007). Recent studies have discovered that excessive bone formation is due to unusual activity of the sclerostin protein, which is a product of the SOST gene in chromosome 17 (Hamersma & Hofmeyr, 2007).

A common clinical feature is gigantism where individuals present with a tall stature during mid-childhood with increased head circumference and excessive weight due to bony overgrowth (Beighton & Hamersma, 1976; Beighton & Hamersma, 1979; Hamersma *et al.*, 2003). Syndactyly is also a characteristic feature of sclerosteosis, which aids in the early identification of sclerosteosis during the neonatal period (Beighton & Hamersma, 1976; Beighton & Hamersma, 1979; Beighton *et al.*, 2007; Hamersma *et al.*, 2003). The severity of syndactyly varies as it ranges from minor skin webbing to complete bony union (Beighton & Hamersma, 1979; Hamersma *et al.*, 2003). Progressive facial distortion during mid-childhood is mostly due to asymmetrical mandibular overgrowth (Beighton & Hamersma, 1976; Beighton & Hamersma, 1979; Beighton *et al.*, 2007;

Hamersma *et al.*, 2003). During the individual's progression towards adulthood gross asymmetrical mandibular enlargement, as well as proptosis and mid-facial hypoplasia, may become evident (Beighton & Hamersma, 1979; Hamersma *et al.*, 2003; Hofmeyr & Hamersma, 2004). The progressive bone formation may cause compression of the 7th cranial nerve in the bony foramina causing entrapment of the 7th cranial nerve which may lead to acute recurrent attacks of facial palsy or facial weakness, mimicking Bell's palsy (Beighton, Hamersma & Brunkow, 2007; Hamersma *et al.*, 2003; Hofmeyr & Hamersma, 2004). A combination of these complications results in speech impairment due to insufficient lip closure and facial weakness (Hamersma *et al.*, 2003; Hofmeyr & Hamersma, 2004).

Elevation of intracranial pressure usually causes bothersome headaches during adolescence (Beighton & Hamersma, 1976; Beighton & Hamersma, 1979; Beighton *et al.*, 2007; Hamersma *et al.*, 2003). The elevation of intracranial pressure is the consequence of progressive reduction of the cranial cavity (Beighton & Hamersma, 1979; Hamersma *et al.*, 2003). Sudden death is a serious risk for patients presenting with elevated intracranial pressure, due to impaction of the medulla oblongata in the foramen magnum (Beighton & Hamersma, 1979; Hamersma *et al.*, 2003).

Some clinical features of sclerosteosis may have a direct influence on the auditory system. Bony overgrowth in the middle ear may cause a conductive hearing loss during the early stages of sclerosteosis (Beighton & Hamersma, 1979; Hofmeyr & Hamersma, 2004). The conductive hearing loss is mainly due to impaired movement of the middle ear ossicles (Hofmeyr & Hamersma, 2004). A sensorineural component may later develop, caused by the closure of both the round and oval windows and compression of the 8th cranial nerve in the internal auditory canals (Beighton & Hamersma, 1979; Hofmeyr & Hamersma, 2004).

Sclerosteosis leads to excessive bony overgrowth on the outer surface of the otic capsule, causing sclerosis of the periosteal layer of the cochlea (Hofmeyr & Hamersma, 2004; Schuknecht, 1993). The metabolic rate of cartilage and lamellar bone in the enchondral bony layer is very slow, thus sclerosteosis does not affect this layer (Jahn, 1988; Schuknecht, 1993). The endosteal bone is also not involved in sclerosteosis, thus the lumen of the cochlea remains unaffected (Jahn, 1988; Schuknecht, 1993).

The symptoms and complications of excessive bony overgrowth are currently managed by surgical treatment (Hofmeyr & Hamersma, 2004). One of the major challenges, however, is the correction of a hearing loss, which has limited success (Beighton & Hamersma, 1979; Hofmeyr & Hamersma, 2004). The encroachment of the dense bone on the round and oval windows needs to be drilled away, which may damage hearing in the high frequencies (Hofmeyr & Hamersma, 2004). Furthermore, recurrent release of the ossicles is a temporary treatment since the progressive nature of the condition means that the ossicles will fixate again (Hofmeyr & Hamersma, 2004).

Although there have been reports of otolaryngological, radiographic and genetic investigations related to sclerosteosis, there have not been any studies to date that have systematically documented the auditory effects related to the condition. In addition, there is a shortage of research regarding nonsurgical management of sclerosteosis despite the fact that most patients usually end up wearing a hearing aid (Beighton & Hamersma, 1979; Hofmeyr & Hamersma, 2004). Consequently it is of importance to describe the auditory presentations of individuals with sclerosteosis to assist future diagnostic investigations and to direct management decisions. The current study therefore provides a cross-sectional description of the audiological profile in patients with sclerosteosis.

3.3. Materials and Methods

The institutional review board of the University of Pretoria approved the study before data collection commenced.

3.3.1. Subjects

A cross-sectional, descriptive research design was followed. Subjects were selected from a database of patients with confirmed diagnoses of sclerosteosis. Of the 36 subjects with diagnosed sclerosteosis alive in South Africa, 18 subjects reside in the Gauteng region and were contacted and invited to participate in the research study. Ten subjects responded and provided written informed consent. The subjects were assessed with a comprehensive audiological test-battery within a single test session lasting approximately two hours. The analysis of results was ear specific and 20 ears were taken into consideration.

3.3.2. Methods

Test procedures included otoscopy, tympanometry, acoustic reflexes, diagnostic pure-tone air- and bone-conduction audiometry, speech audiometry, DPOAEs, ABRs and CT scans. The otoscopic evaluation (ReddyLite™) was conducted to visualise any obstructive debris in the ear canals, which may be contra-indicative for other tests. Tympanometry (GSI Tymptstar, Grason-Stadler, Madison, WI, USA) was conducted bilaterally to measure static compliance, middle ear pressure and ear canal volume (ECV). The modified Jerger classification system for tympanometry was used to interpret the tympanogram type (Jerger, 1970). Ipsi- and contra-lateral acoustic reflexes were measured using a 226 Hz probe tone frequency with pure tone octave stimuli from 500 to 2000 Hz for ipsi-lateral reflex recordings and 500 to 4000 Hz for contra-lateral reflex recordings. The stimulus was initially presented at 75 dB HL. The intensity was increased in 10 dB steps and decreased in 5 dB steps until a reflex was elicited. A reflex threshold was the last visible deflection of 0.02 or more and was only accepted if it was repeatable.

A clinical audiometer (GSI 61, Grason-Stadler, Milford, NH, USA) was used to conduct pure tone air conduction, bone conduction and speech audiometry. All testing was conducted in a sound proof booth using supra-aural earphones (Telephonics, TDH-49P) for air conduction audiometry and a bone oscillator (Radioear, B-71) for bone conduction audiometry. Octave frequencies between 250 to 8000 Hz were used for pure tone air conduction audiometry, while the octave frequencies between 250 to 4000 Hz were utilized for bone conduction audiometry. The pure tone and bone conduction threshold seeking procedure was according to the modified Hughson-Westlake method (Carhart & Jerger, 1959; Hughson & Westlake, 1944). The PTA (500 to 2000 Hz) was used to categorize severity and audiometric configuration of hearing impairment according to the criteria provided by Jerger (Jerger & Jerger, 1980).

Speech audiometry was presented with live voice in Afrikaans, as all the subjects are Afrikaans speaking. The *Afrikaanse Spondee Woordelys* (Laubscher & Tesner, 1966) was used to obtain SRT. A list of six spondee words was presented until a subject detected 50% of the words correctly. The *Afrikaans Foneties Gebalanseerde Woordelys* (Laubscher & Tesner, 1966) was used to obtain SRS across intensities. A list of 25 phonetically balanced words was presented at three different intensities in order to obtain a percentage of words detected correctly. Agreement between the PTA and speech

thresholds is considered reliable when within +/- 7 dB of each other (Hall & Mueller, 1997).

DPOAEs were measured using (Navigator Pro system, Biologic Systems Corp.) a 1.22 frequency ratio (f_2/f_1) at differential sound pressure levels ($L_1=65\text{dB SPL}$, $L_2=55\text{dB SPL}$). The DPOAE amplitude was measured at the frequencies $2f_1-f_2$ with f_2 varying from 1008 to 8016 Hz (1008, 1266, 1570, 1992, 2508, 3164, 4008, 5063, 6352 and 8016 Hz). The average noise floor was approximated around the $2f_1-f_2$ frequency. The spectrum ranges for the upper frequency limit was 10 000 Hz and the decibel ranges at 100 dB. The DP-Gram analysis ranges maximized at 70 dB with a minimum level of -30 dB. The referencing data used was according to the Vanderbilt 65/55, 95 to 5th percentile norms. Interpretation of data followed the normative data system, according to Hall (Hall & Mueller, 1997).

The same system (Navigator Pro system, Biologic Systems Corp.) was used to measure the ABR in each subject. The ABR was elicited using air conduction click stimuli with a patient lying supine on a bed in a soundproof booth. Following skin preparation, three electrodes were placed with the non-inverting electrode on the high forehead (Cz), the inverting electrode on the test earlobe and the ground electrode on the contra-lateral earlobe. Impedance was kept $<5\text{ k}\Omega$. Subjects were instructed to lie comfortably on a bed with their eyes closed. Rarefaction clicks were delivered monaurally through insert earphones. The stimulus rate was 11.1 stimuli/sec. Subjects were tested at an intensity of 90 dB nHL with a recording time window of 21 ms. The maximum amount of averaged recordings was 2000 sweeps. Artifact rejection was set at 23.3 μV and the recordings were filtered between 100 and 3000 Hz. Latencies of Waves I, III and V were measured and interpreted by three experienced clinicians (Hall & Mueller, 1997; Hall & Swanepoel, 2010).

CT scans were conducted on 9/10 subjects (one subject was not able to attend the appointment). The CT scans were conducted and interpreted by an experienced radiologist (5th author) at the Muelmed Mediclinic in Pretoria, South Africa.

3.3.3. Data analysis

Test results were examined in the test population. Descriptive analyses were used to illustrate the average distributions, i.e. means, standard deviations, minimum and maximum values. The Independent Samples Mann-Whitney Test was used to assess if older subjects had larger ABGs than younger subjects (5% significance level was used).

3.4. Results and Analysis

The mean age of the subjects (Table 3.1) with sclerosteosis was 32 years (± 20.2 SD), ranging from 10 to 72 years (4 male, 6 female). None of the subjects reported otalgia but tinnitus was reported by 70% (n=7) of subjects (two unilateral and five bilateral) and all subjects reported dizziness. The dizziness was attributed to low blood pressure in 60% (n=6) of subjects. Subjective dizziness associated with hearing was reported by 40% (n=4) of the subjects. One third (30%; n=3) of subjects reported problems with balance.

TABLE 3.1.

Description of subjects according to age, gender and tympanometry results. ECV = Ear canal volume.

Subjects	Age	Gender	Tympanogram Right	ECV Right	Tympanogram Left	ECV Left
1	72	Female	A	1.7	As	2.4
2	55	Female	B	0.5	A	1.1
3	20	Male	A	2.7	As	1.8
4	19	Female	B	0.8	B	1.8
5	45	Male	B	1.8	A	2.1
6	21	Female	As	0.9	A	1.8
7	14	Male	B	3.7	A	2.4
8	10	Male	A	1.6	B	1.7
9	40	Female	A	1.4	A	1.6
10	24	Female	A	1.4	As	0.9

Otoscopic examination indicated a clear external auditory meatus, free from any debris and a healthy tympanic membrane in all subjects. Tympanometry (Table 3.1) results included Type A tympanograms for 50% (n=10) of ears with large ECV (n=8) and normal ECV (n=2). Type As (n=4) and type B (n=6) tympanograms constituted 50% of ears. One type B tympanogram had an ECV <0.6 ml. Two of the ears had normal (1.0 – 1.5 ml) ECV, but the other three had ECV >1.7 ml. Two type As tympanograms had ECV >1.5 ml and two ears had ECV <1.0 ml. Ipsi-lateral and contra-lateral acoustic reflexes were absent in all subjects.

Degrees of hearing loss varied from moderate (5%; n=1), severe (55%; n=11) to profound (40%; n=8) across ears. Hearing losses were symmetrical in six subjects and asymmetrical (comparing PTAs) in four subjects. Hearing loss configurations ranged from rising (15%), sloping (35%), and air conduction thresholds peaked at 2000 Hz (50%) (Figure 3.1; Table 3.2). These 2000 Hz air conduction peaks indicated a mean difference between the thresholds at 1000 Hz and 2000 Hz of 15 dB (± 7.89 SD, range 5 to 25 dB HL), whilst the mean difference between the thresholds at 2000 Hz and 4000 Hz was 20 dB (± 11.28 SD, range 5 to 45 dB HL). Speech audiometry results (SRT and SRS) were compared with the PTA in Table 3.2.

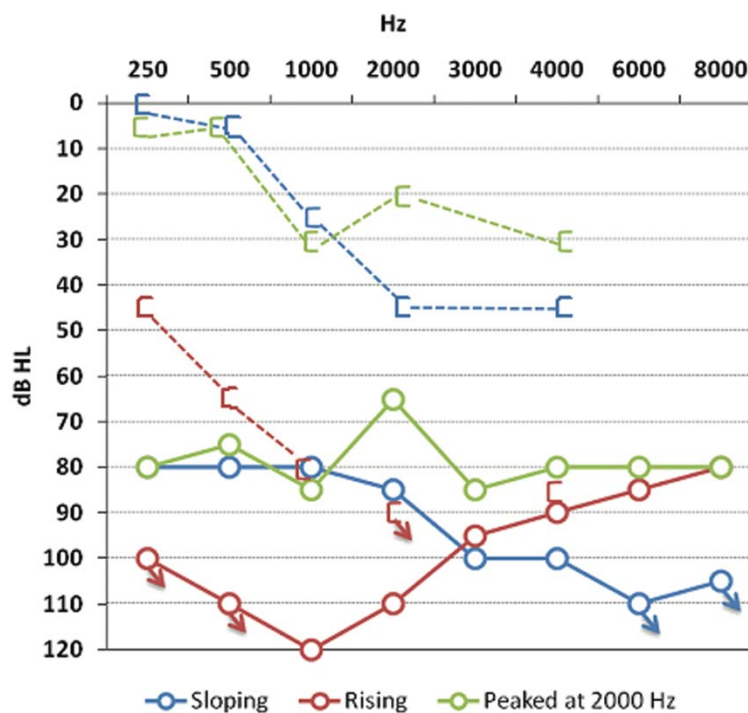


Fig 3.1.

Examples of three hearing loss configurations recorded in the sample of sclerosteosis subjects.

TABLE 3.2.

Pure tone and speech audiometry findings in subjects with sclerosteosis (n=20 ears). *PTA = Pure tone average; SRT = Speech reception threshold; SRS = Speech recognition score.*

Subjects	Ear	Degree of HL	Configuration	Type	PTA	SRT	SRT/PTA	SRS
1	L	Profound	Peaked	Mixed	83	90	7	0%/105 dB
	R	Severe	Peaked	Mixed	75	60	5	70%/100 dB
2	L	Severe	Sloping	Mixed	65	65	0	100%/85 dB
	R	Severe	Sloping	Mixed	71	75	4	100%/95 dB
3	L	Profound	Peaked	Mixed	93	90	-3	100%/105 dB
	R	Profound	Sloping	Mixed	94	85	-9	100%/105 dB
4	L	Severe	Peaked	Mixed	71	70	1	100%/90 dB
	R	Severe	Peaked	Mixed	78	80	2	100%/90 dB
5	L	Profound	Sloping	Mixed	89	90	1	100%/100 dB
	R	Severe	Peaked	Mixed	61	65	4	100%/75 dB
6	L	Moderate	Peaked	Mixed	45	45	0	100%/55 dB
	R	Profound	Sloping	Mixed	85	75	-10	100%/85 dB
7	L	Severe	Peaked	Mixed	75	80	5	100%/90 dB
	R	Profound	Rising	Mixed	80	85	5	100%/105 dB
8	L	Severe	Peaked	Mixed	74	55	-19	100%/75 dB
	R	Severe	Rising	Mixed	69	65	4	100%/85 dB
9	L	Severe	Sloping	Mixed	74	80	6	100%/90 dB
	R	Severe	Sloping	Mixed	70	80	10	100%/90 dB
10	L	Profound	Rising	Mixed	106	>105	>1	0%/105 dB
	R	Profound	Peaked	Mixed	100	>110	>10	0%/110 dB
Mean(SD)	-	-	Peaked	Mixed	75.1(14.12)	74.2 (12.86)	0.7 (7.09)	93%/90 dB
Min	-	-	-	-	45	45	-19	-
Max	-	-	-	-	106	90	10	-

Mixed hearing losses characterised all ears across the frequencies of 500 to 4000 Hz (Table 3.2 and 3.3). One third of the ears (30%) demonstrated ABGs declining towards the higher frequencies. Subjects were divided into two age groups to determine if there was a difference in ABGs related to age. The first group ranged from 10 to 39 years (12 ears) and the second group from 40 to 72 years (8 ears). Mean ABG results for Group 1 at 500 Hz was 47 dB (\pm 14.7 SD), 1000 Hz was 39 dB (\pm 15 SD), 21 dB (\pm 21 SD) at 2000 Hz, 32 dB (\pm 18 SD) at 4000 Hz. The mean ABG for Group 2 at 500 Hz was 36 dB (\pm 20 SD), 1000 Hz was 26 dB (\pm 16 SD), 2000 Hz was 13 dB (\pm 13 SD) and 4000 Hz was 19 dB (\pm 19 SD). Despite showing larger ABGs in the older age group, the descriptive difference was not statistically significant ($p > .05$; Independent Samples Mann-Whitney Test), but may partly be due to the small sample size.

TABLE 3.3.
Air-bone gaps for subjects with sclerosteosis (n=20 ears).

Subjects	Ear	500 Hz	1000 Hz	2000 Hz	4000 Hz	Average
1	L	<15	10	0	15	8.3
	R	15	10	10	<35	11.7
2	L	30	25	10	20	21.3
	R	30	20	5	20	18.8
3	L	65	50	30	45	47.5
	R	65	50	25	<25	46.7
4	L	50	50	35	30	41.3
	R	65	55	45	50	53.8
5	L	75	55	40	55	56.3
	R	45	35	10	0	22.5
6	L	30	0	0	35	16.3
	R	50	45	60	60	53.8
7	L	45	35	0	40	30
	R	40	45	15	10	27.5
8	L	25	40	15	15	23.8
	R	55	35	0	25	28.8
9	L	25	40	20	25	27.5
	R	30	15	5	0	12.5
10	L	45	40	<20	5	30
	R	25	25	0	<30	16.7
Average(SD)	-	45.5 (16.9)	34.7 (16.2)	18.1 (17.7)	27.8 (18.7)	30.4 (15.1)
Min	-	15	0	0	0	8.3
Max	-	75	55	60	60	56.3

No repeatable DPOAEs were recorded in any of the ears across all frequencies. Despite precautions taken to minimise internal and external noise during the ABR recordings, the average percentage of the ABR recordings rejected due to excessive EEG noise (artifacts)

across the 20 ears were high (Table 3.4). Only four recordings of 2000 sweeps could be made with less than 20% of the sweeps being rejected due to excessive EEG activity. No waves were recorded in 60% (n=12) of ears. Waves I, III and V were recorded in 30% (n=6) of ears. Waves I and V were recorded in 10% (n=2) ears with wave III being absent.

TABLE 3.4.

Auditory brainstem response (ABR) results in subjects with sclerosteosis (n=20 ears).

Subjects	90 dB nHL	Artifacts*	Latencies:	Wave I	Wave III	Wave V	No waves
1	Left	32%		-	-	-	X
	Right	41%		-	-	-	X
2	Left	47%		2.01	4.39	6.32	
	Right	33%		2.20	-	5.89	
3	Left**	24%		-	-	-	X
	Right**	40%		-	-	-	X
4	Left	21%		-	-	-	X
	Right	27%		3.46	-	7.57	
5	Left	85%		2.01	4.32	6.07	
	Right	25%		-	-	-	X
6	Left	15%		2.08	3.20	6.20	
	Right	2%		2.08	3.76	6.76	
7	Left	17%		-	-	-	X
	Right	24%		-	-	-	X
8	Left	79%		-	-	-	X
	Right	85%		2.89	5.14	6.89	
9	Left	57%		-	-	-	X
	Right	51%		2.06	4.23	6.32	
10	Left	16%		-	-	-	X
	Right	63%		-	-	-	X
Mean (SD)	-	39% (24%)	-	2.35 (0.5)	4.17 (0.6)	6.50 (0.5)	-

*The average artifacts and rejection sweeps present during each ABR recording.

**A single subject's ABR recording conducted at 95 dB nHL.

CT scans were conducted on 9/10 subjects. Anatomical structures analysed and reported in Table 3.5 indicate abnormalities of the external auditory canal, tympanic membrane, middle ear space, ossicles, oval window, round window, and the internal auditory canal (Figure 3.2).

TABLE 3.5.

Anatomical abnormalities according to *Computed tomography* (CT) scan analyses of the auditory system in sclerosteosis (n=18 ears).

Anatomical structures	Abnormal	Abnormalities recorded
External auditory canal	11% (n=2)	Exostosis Slightly narrow in mid-portion
Middle ear space	50% (n=9)	Very small Small Obliterated Filled with soft tissue Errated
Tympanic Membrane	11% (n=2)	Tympanosclerosis Obliterated
Malleus	67% (n=12)	Fixated Loose Remnant Absent
Incus	83% (n=15)	Fixated Dislocated Absent
Stapes	72% (n=13)	Loose Thickened Deep, fixated Fixated Absent
Oval window	89% (n=16)	Closed and deep Open and deep Presence of soft tissue Bony overgrowth Closed
Round window	94% (n=17)	Long and narrow Bony overgrowth Closed
Internal auditory canal	89% (n=16)	Narrow-open Slightly narrow-open Very narrow-open Narrow-open (trumpet shaped) Closed



Fig. 3.2a

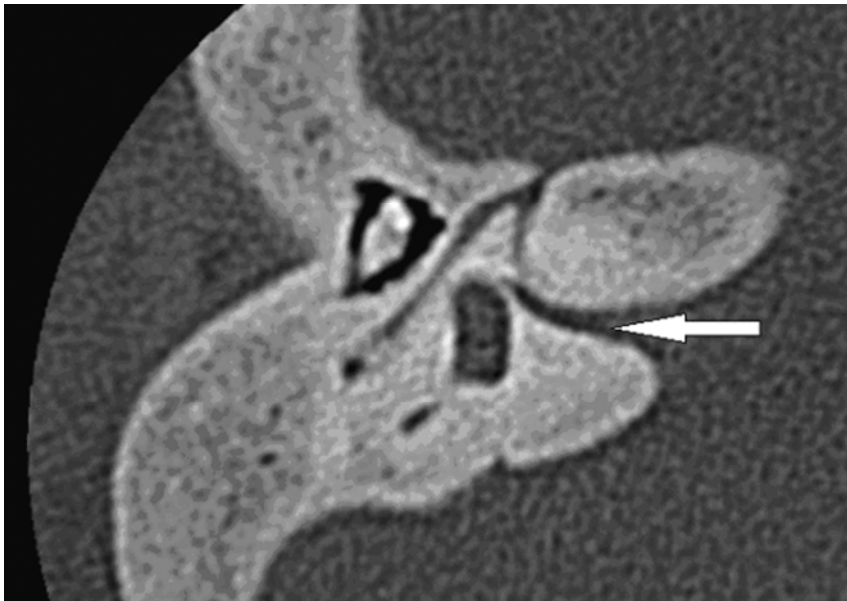


Fig. 3.2b

Fig. 3.2.

Axial CT through the internal auditory canals. Fig 3.2a demonstrates a normal internal auditory canal in a normal developed ear (white arrow) and Fig 3.2b a narrowed internal auditory canal (white arrow) in sclerosteosis. The auditory nerve is compressed in the internal auditory canal.

3.5. Discussion

This is the first study to provide a comprehensive auditory profile of subjects with sclerosteosis including functional measures of the auditory system and imaging studies. Results indicate mixed hearing losses as typical of all subjects with structural abnormalities in the middle ear, oval and round windows of the cochlea and internal auditory canal.

Beighton and Hamersma were the first investigators to document the clinical, radiological and genetic features of sclerosteosis (Beighton & Hamersma, 1976). In their study they combined the documentation of subjects affected by sclerosteosis to describe their clinical features. Temporal bone and radiology scans in sclerosteosis showed that sensorineural hearing loss was due to the closure of the oval and round windows, as well as narrowing of the internal auditory canal, with resultant compression of the auditory nerve (Beighton & Hamersma, 1976; Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004). Current study findings concur with these earlier reports showing internal auditory canals narrowed to some degree in the majority of ears (n=16/18). Several anatomical deformities, including closed, deep, narrow and long oval and round windows, were noted in the current study and were attributed to both soft tissue and bony overgrowth.

Normal middle ear functioning, as measured by tympanometry, was indicated for 50% of ears, whilst 50% showed abnormal functioning with type As and type B tympanograms. CT scans, however, indicate abnormalities of the malleus (67%, n=12), incus (83%, n=15) and stapes (72%, n=13) of which the majority of ossicles were fixated. The ossicular abnormalities were attributed to obliteration of the middle ear space, due to bony overgrowth and soft tissue. Interestingly, normal tympanograms could still be recorded, suggesting that the major conductive hearing loss component may be related to the stapes fixation. Hamersma and Hofmeyr also reported middle ear abnormalities through CT scans and abnormalities visualised during surgery (Hamersma & Hofmeyr, 2007). The authors stated that the middle ear condition is surgically treatable, but that improvements in hearing were expected to be temporary, as bone encroaches on the middle ear and again fixates the ossicles (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004).

Abnormal bony growth in the middle ear and round and oval windows of the cochlea, associated with sclerosteosis, and the resulting audiological findings show similarities to otosclerosis. Hearing loss configurations in sclerosteosis included rising, sloping and air conduction thresholds peaking at 2000 Hz. Yasan's research findings on the Carhart's notch (2000 Hz) had been documented in various disorders such as otitis media, tympanosclerosis and congenital ossicular abnormalities which also relates to the air conduction peak at 2000 Hz in sclerosteosis (Yasan, 2007). Air conduction configurations in sclerosteosis evidence the middle ear obliterations, fixation or absence of various middle ear ossicles, cochlear abnormalities at the round and oval windows, as well as compression of the internal auditory canal. Slight asymmetrical hearing losses were reported in a minority of subjects (n=4). No obvious difference was, however noticeable between the structures of the middle ear, oval and round windows of the cochlea, and internal auditory canal as observed on the CT scans between these sets of ears. The asymmetrical hearing losses therefore are most likely due to functional impairment in the auditory system or structural abnormalities not visualised with CT scans.

Previous reports demonstrated ABGs related to otosclerosis as large as 40 dB in the low frequencies, decreasing towards 2000 Hz where the Carhart's notch is typically found (Azlan, Asma & Saim, 2010). Mixed hearing losses have been recorded in isolated cases of otosclerosis involving the middle ear and cochlea (Velegrakis, 2011). Middle ear, oval and round window involvement is common in otosclerosis as well as sclerosteosis. Fixation of the middle ear ossicles and closure of the round and oval windows have been reported in both conditions, but the degree to which these structures are affected leads to a more severe sensorineural hearing loss in sclerosteosis (Hofmeyr & Hamersma, 2004; Perez, De Almeida, Nedzelski, Chen, 2009; Thomas, Minovi, Dazert, 2011; Velegrakis, 2011). Additionally, sclerosteosis include involvement of the internal auditory canal, which is not typical in otosclerosis. Aging and otosclerosis in relation to audiometric findings have indicated that air conduction and bone conduction thresholds deteriorate at all frequencies with increasing age (Topsakal *et al.*, 2006). In the current study the ABGs also showed a general increase with age but were not statistically significant.

Van Buchem's disease and sclerosteosis both belong to the family of osteopetroses, characterised by skeletal density and bone modelling (Beighton *et al.*, 1977). Clinical features of Van Buchem's disease closely resembles sclerosteosis, but to a milder degree. The auditory profile on audiometric testing for Van Buchem's disease has not been systematically documented, but hearing loss has been reported in 40% of subjects presenting with Van Buchem's disease, as opposed to 92% in sclerosteosis (Beighton *et al.*, 1977; Beighton *et al.*, 1984). In the current study, all subjects with sclerosteosis presented with a mixed hearing loss, in contrast to the 25 subjects investigated by Beighton *et al.* of which 92% had mixed hearing losses (Beighton *et al.*, 1984).

Osteogenesis imperfecta (OI) is another disorder with similarities to sclerosteosis in terms of auditory involvement related to bone abnormalities. OI is a bone mineral density disorder affecting the connective tissue involving the musculoskeletal system, causing otosclerotic-like lesions affecting the ears (Swinnen, De Leenheer, Goemaere *et al.*, 2012). Sclerosteosis and OI share middle ear abnormalities and involvement of the oval window of the cochlea. Ossicular discontinuity and fixation of the stapes have been reported in OI as in sclerosteosis, with the middle ears affected by abnormal bony growth in both disorders (Hofmeyr & Hamersma, 2004; Swinnen, De Leenheer, Goemaere *et al.*, 2012). The oval window is affected by encroachment of bony overgrowth in both disorders, but additionally the round window is also affected in sclerosteosis (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004; Swinnen, De Leenheer, Goemaere *et al.*, 2012). The sensorineural hearing loss in OI is a result of abnormal bone encroachment causing haemorrhage into the labyrinth, resulting in cochlear hair cell damage (Swinnen, De Leenheer, Goemaere *et al.*, 2012). In comparison, sensorineural hearing loss in sclerosteosis has been attributed to closure of the round and oval windows, as well as narrowing of the internal auditory canal which compromises auditory nerve functioning (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004). Swinnen documented a variety of mild to profound mixed hearing losses (23 – 78%) in IO, whilst the current study recorded only moderate to profound mixed hearing losses (100%) in sclerosteosis (Swinnen, 2012). In contrast to sclerosteosis, IO has no documented effect on the internal auditory canal (Swinnen, De Leenheer, Goemaere *et al.*, 2012).

ABR recordings in sclerosteosis were challenging, as excessive EEG activity caused high numbers of artifacts and rejected sweeps, resulting in unreliable ABR recordings. ABR waves were absent at a maximum intensity of 90 dB nHL in most ears (n=12), but when present, were significantly delayed. The CT scans confirm conductive and sensorineural abnormalities, due to a combination of middle ear, round and oval window closure of the cochlear and internal auditory canal involvement (Musiek, Shinn, Jirsa, 2007). CT scans indicated that only one subject's internal auditory canal was unaffected. The ABR results for this subject, in contrast to results for most other subjects, presented with waves I, III and V. The presence of all ABR waves was found in only four other ears, for which CT scans were completed on three of these four subjects. The respective CT scans demonstrated that the internal auditory canals were only mildly affected by slight narrowing. ABR waves in these cases were also delayed, most likely as a result of the conductive hearing loss and some sensorineural contribution (Musiek *et al.*, 2007). Two of the remaining 14 ears had an absent ABR wave III and the remaining 12 ears had no ABR waves. The CT scans showed that 16 ears had internal auditory canals that were narrow, very narrow (slightly open), or completely closed. Retro-cochlear auditory involvement was indicated by the phonetically-balanced performance-intensity function ('roll-over') in two subjects (Miranda & Pichora-Fuller, 2002; Jerger & Hayes, 1977; Stach, Hornsby, Rosenfeld, De Chicchis, 2009). CT scans for these subjects showed very narrow internal auditory canals and no ABR waves in one subject and an absent wave III for the second subject. ABR and CT scan findings are in agreement with possible retro-cochlear involvement indicated by the speech audiometry results.

Surgical decompression of the internal auditory canal in young children (before the age of 6 years) is recommended as early as possible, to prevent narrowing of the internal auditory canal and damage to the auditory nerve (Hamersma & Hofmeyr, 2007). If surgical decompression of the internal auditory canal proves to have sustainable success and the auditory nerve is undamaged, future studies should document the possible management of hearing loss with cochlear implants. It would be hazardous to decompress the internal auditory canal in older subjects since the auditory nerve may sustain damage during the surgical intervention. Auditory brainstem implants (ABI) may be a possible option for the

management of retro-cochlear involvement, but future investigations need to confirm the benefit of ABIs as a last resort treatment of sclerosteosis related auditory dysfunction. Conservative management of hearing loss includes a conventional hearing aid or a bone anchored hearing aid depending on the severity of the loss (Hofmeyr & Hamersma, 2004).

3.6. Conclusion

Subjects with sclerosteosis present with anatomical abnormalities of the middle ear, oval and round windows of the cochlea and internal auditory canal. These abnormalities result in moderate to profound mixed hearing losses. Similarities in the audiometric findings, when compared to otosclerosis and other conditions characterised by abnormal bony growth were evident, although sclerosteosis related auditory dysfunction is typically more severe. Abnormalities of the oval and round windows of the cochlea and internal auditory canal cause sensorineural involvement, as evidenced by absent DPOAEs and absent or abnormal ABR findings. ABR and speech audiometry may assist in differentiating cases with significant involvement of the internal auditory canal. The progressive abnormal bony overgrowth, which is the hallmark of sclerosteosis, leads to functional impairment at various levels in the auditory system. Current findings provide a comprehensive auditory profile for sclerosteosis and may be utilised alongside future research findings to direct criteria and audiological indications for surgical and audiological intervention.

4. DISCUSSION AND CONCLUSION

4.1. Discussion of Results

This was the first study to provide a comprehensive auditory profile, including functional measures of the auditory system and imaging studies of subjects with sclerosteosis. Findings indicated that mixed hearing losses were a general feature of sclerosteosis with structural abnormalities of the middle ear, oval and round windows of the cochlea and internal auditory canals.

Beighton and Hamersma (1976) were some of the leading investigators to document clinical, radiological and genetic features of sclerosteosis (Beighton & Hamersma, 1976). In their study they combined the documentation of subjects affected by sclerosteosis to describe their clinical features. Temporal bone and radiology scans in sclerosteosis showed that sensorineural hearing loss was due to the closure of the oval and round windows, as well as narrowing of the internal auditory canal with resultant compression of the auditory nerve (Beighton & Hamersma, 1976; Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004). Current study findings concurred with these earlier reports, showing internal auditory canals narrowed to some degree in almost all ears (n=16/18). Several anatomical deformities included closed, deep, narrow and long oval and round windows, noted in the current study and were attributed to both soft tissue and bony overgrowth.

In the current study normal middle ear functioning, as measured by tympanometry, were indicated for 50% of ears, whilst 50% showed abnormal functioning with type As and type B tympanograms. CT scans, however, indicated abnormalities of the malleus (67%, n=12), incus (83%, n=15) and stapes (72%, n=13) of which the majority of ossicles were fixated. The ossicular abnormalities were attributed to obliteration of the middle ear space due to bony overgrowth and associated soft tissue. Interestingly, normal tympanograms could still be recorded in half of ears, suggesting that the major conductive hearing loss component might relate to ossicular chain and stapes fixation. Type A tympanograms had previously been reported in middle ear pathologies involving the ossicular chain (Nadol & Schuknicht, 1993), suggesting that type A tympanograms obtained in sclerosteosis did not exclude

conductive hearing loss by any means. Interpretation of tympanograms in sclerosteosis should be done cautiously and always in combination with other test findings. It was recommended that high frequencies probe tones (678 and 1000 Hz) and wide band reflectance also be explored for assessing middle ears in sclerosteosis. The additional middle ear tests might provide more information on the middle ear dysfunction, mass and stiffness reactance of the middle ear ossicles when considering the components of susceptance and conductance separately. (Lantz, Petrak, Prigge, 2004; Hall & Swanepoel, 2010; Shahnaz *et al.*, 2009).

Hamersma and Hofmeyr (2004 & 2007) also previously reported middle ear abnormalities through CT scans and saw these middle ear abnormalities during surgery (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004). The authors reported that the middle ear condition was surgically treatable, but that improvements in hearing were expected to be temporary, as bone encroached on the middle ear and fixated the ossicles again (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004).

Abnormal bony growth in the middle ear and round and oval windows of the cochlea, associated with sclerosteosis, and the resulting audiological findings showed similarities to a more common condition such as otosclerosis. Previous reports demonstrated ABGs related to otosclerosis as large as 40 dB in the low frequencies, decreasing towards 2000 Hz where the Carhart's notch was typically found (Azlan *et al.*, 2010). The same ABG pattern was observed in some cases of sclerosteosis (50%). ABGs as large as 75 dB in the low frequencies were observed and decreased towards 2000 Hz demonstrating a type of Carhart's notch. Yasan (2009) indicated that the Carhart's notch was not only found in otosclerosis, but in various disorders such as otitis media, tympanosclerosis and congenital ossicular abnormalities, as the movement to the footplate of the stapes was compromised in these disorders (Yasan, 2009). Huizing (1964) carefully documented the audiometric configurations in otitis media. He explained that in some cases of otitis media the footplate of the stapes fixated, causing the Carhart's notch (Huizing, 1964). Bauer (1964) documented the Carhart's notch in tympanosclerosis attributing it to stapedia fixation, causing interruption to the inertia of the ossicular chain (Bauer, 1964). More recently Somers and

colleagues (Somers, Declau, Kuhweide, Robillard, 2007) also explained that the Carhart's notch, typically seen in otosclerosis, could be mimicked by other otological diseases. These authors documented a list of otological diseases that mimicked the bone-conduction of Carhart's notch which included otitis media, post-traumatic stapes fixation, malleus head fixation, minor malformations of the middle ear, abnormal perilymph pressure, Paget's disease and OI. The research conducted on these disorders also indicated that in some cases an air-conduction peak at 2000 Hz, demonstrating stapedia fixation, could be observed (Somers *et al.*, 2007; Yasan, 2009). The results of these studies related to sclerosteosis, as a 2000 Hz air-conduction peak (50%) was also observed.

Slight asymmetrical hearing losses were reported in a minority of subjects (n=4). No obvious difference was however noticeable between the structures of the middle ear, oval and round windows of the cochlea, and internal auditory canal as observed on the CT scans between these sets of ears. The asymmetrical hearing losses therefore were most likely due to functional impairment in the auditory system or structural abnormalities not visualised with CT scans.

Mixed hearing losses in sclerosteosis involved the middle ear, oval and round windows of the cochlea and the internal auditory canal. Mixed hearing losses had been recorded in isolated cases of otosclerosis involving the middle ear and cochlea (Velegrakis, 2011). Sclerosteosis and otosclerosis shared similarities in audiometric findings influenced by abnormalities of the middle ear and oval and round windows of the cochlea. There were however differences to the progression of the conditions. Otosclerosis affected the enchondral bone of the otic capsule, causing bone resorption and replacement with dense sclerostic bone (Perez *et al.*, 2009; Thomas *et al.*, 2011; Velegrakis, 2010). This process caused obliteration of the oval window and in some cases progressed to the inner ear affecting the entire temporal bone (Perez *et al.*, 2009; Thomas *et al.*, 2011; Velegrakis, 2010). Sclerosteosis, however, led to excessive bony overgrowth of the otic capsule, causing sclerosis of the periosteal layer of the cochlea (Hofmeyr & Hamersma, 2004; Schuknecht, 1993). The metabolic rate of cartilage and lamellar bone in the enchondral bony layer was very slow, thus sclerosteosis did not affect this layer (Jahn, 1988;

Schuknecht, 1993). The endosteal bone was also not involved in sclerosteosis, thus the lumen of the cochlea remained unaffected (Jahn, 1988; Schuknecht, 1993). The difference between the two conditions was that sclerosteosis did not affect the cochlea, but additionally involved the internal auditory canal and other bony parts of the human body, whereas in extreme cases of otosclerosis the condition was found across the entire temporal bone (Hofmeyr & Hamersma, 2004; Thomas *et al.*, 2011). Aging and otosclerosis, in relation to audiometric findings, indicated that air-conduction and bone-conduction thresholds deteriorate at all frequencies with increasing age (Topsakal *et al.*, 2006). In the current study the ABGs also suggested a general increase with age but was not statistically significant, which might be due to the small sample size.

Another disorder that showed similarities to sclerosteosis was Van Buchem's disease. Both these conditions belonged to the family of osteopetroses, characterised by skeletal density and bone modelling (Beighton *et al.*, 1977). Clinical features of Van Buchem's disease closely resembled sclerosteosis, but to a milder degree as prognosis in Van Buchem's disease was benign (Beighton *et al.*, 2007). The prognosis in sclerosteosis was potentially lethal, due to aggressive bone formation (Beighton *et al.*, 2007). The auditory profile on audiometric testing for Van Buchem's disease had not been systematically documented, but hearing loss had been reported in 40% of subjects presented with Van Buchem's disease, as opposed to 92% in a previous study of sclerosteosis (Beighton *et al.*, 1984; Beighton *et al.*, 1977). In the current study, all subjects with sclerosteosis presented with a mixed hearing loss, in contrast to the 25 subjects investigated by Beighton *et al.* (1984) of which a small number (8%) did not present with deafness. Some subjects were diagnosed with mild sclerosteosis (20%), but no further reasons were given for the 8% of subjects who did not present with deafness (Beighton *et al.*, 1984).

OI was also a disorder related to bone abnormalities with some similarities to sclerosteosis in terms of auditory involvement and the nature of the disease. OI was a bone mineral density disorder affecting the connective tissue involving the musculoskeletal, causing otosclerotic-like lesions affecting the ears (Swinnen, De Leenheer, Goemaere *et al.*, 2012). Sclerosteosis and OI shared middle ear abnormalities and involvement of the oval window of

the cochlea. Ossicular discontinuity and fixation of the stapes had been reported in OI as in sclerosteosis, with the middle ears affected by abnormal bony growth in both disorders (Hofmeyr & Hamersma, 2004; Swinnen, De Leenheer, Goemaere *et al.*, 2012). The oval window was affected by encroachment of bony overgrowth in both disorders, but additionally the round window was also affected in sclerosteosis (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004; Swinnen, De Leenheer, Goemaere *et al.*, 2012). The sensorineural hearing loss in OI was a result of abnormal bone encroachment that caused haemorrhage into the labyrinth resulting in cochlear hair cell damage (Swinnen, De Leenheer, Goemaere *et al.*, 2012). In comparison, sensorineural hearing loss in sclerosteosis had been attributed to closure of the round and oval windows, as well as narrowing of the internal auditory canal which compromised auditory nerve functioning (Hamersma & Hofmeyr, 2007; Hofmeyr & Hamersma, 2004). Swinnen (2012) documented a variety of mild to profound mixed hearing losses (23 – 78%) in IO, whilst the current study recorded only moderate to profound mixed hearing losses (100%) related to sclerosteosis (Swinnen, 2012). In contrast to sclerosteosis, IO had no documented effect on the internal auditory canal (Swinnen, De Leenheer, Goemaere *et al.*, 2012).

ABR recordings in sclerosteosis were challenging due to excessive EEG activity resulting in high numbers of rejected sweeps yielding unreliable ABR recordings. ABR waves were absent at a maximum intensity of 90 dB nHL in most ears (n=12/20), but when present, were significantly delayed. The CT scans confirmed conductive and sensorineural abnormalities due to a combination of middle ear, round and oval window closure of the cochlear and internal auditory canal involvement (Musiek *et al.*, 2007). CT scans indicated that only one subject's internal auditory canal was unaffected. The ABR results for this subject, in contrast to results for most other subjects, presented with waves I, III and V. The presence of all ABR waves were found in only four other ears for which CT scans were completed on three of these four subjects. The respective CT scans demonstrated that the internal auditory canals were only mildly affected with slight narrowing. ABR waves in these cases were also delayed, most likely as a result of the conductive hearing loss and some sensorineural contribution (Musiek *et al.*, 2007). Two of the remaining 14 ears had an absent ABR wave III and the remaining 12 ears had no ABR waves. The CT scans showed that 16 ears had

internal auditory canals that were narrow, very narrow (slightly open), or completely closed. Retro-cochlear auditory involvement was indicated by the phonetically-balanced performance-intensity function ('roll-over') in two subjects (Jerger & Hayes, 1977; Miranda & Pichora-Fuller, 2002; Stach *et al.*, 2009). CT scans for these subjects showed very narrow internal auditory canals and no ABR waves in one subject and an absent wave III in the second subject. ABR and CT scan findings concurred with the possibility of retro-cochlear involvement indicated by speech audiometry results.

4.2. Clinical Implications and Recommendations

CT scans visually presented middle ear abnormalities (fixated ossicles and obliterated middle ear spaces) of each subject with sclerosteosis. Even though the subjects presented with severe middle ear abnormalities, tympanometry findings indicated that 50% of ears presented with type A tympanograms were usually indicative of normal middle ear functioning. The tympanometry findings were inconsistent considering the degree to which the excessive bone had encroached on the middle ear. This study pointed out that conventional tympanometry testing was not appropriate to assist in diagnosis of middle ear pathology and conductive hearing loss typical of sclerosteosis, due to false negative findings. High frequency probe tone tympanometry and wideband reflectance were alternative middle ear test procedures that should be explored when evaluating sclerosteosis. The high frequencies probe tones (678 and 1000 Hz) might aid in assessing the pathology of the middle ear, as it supplies information on the mass and stiffness reactance of the middle ear, especially the middle ear ossicles (Lantz, Petrak, Prigge, 2004). Wideband reflectance might also be useful to better describe the reflectance of the middle ear system through a wideband middle ear power frequency range of 258 to 6000 Hz. These recordings might provide more information on middle ear dysfunction and conductive hearing loss in sclerosteosis (Hall & Swanepoel, 2010; Shahnaz *et al.*, 2009).

The results of this study also indicated that mixed hearing losses were present in all subjects with sclerosteosis. The mixed hearing losses were caused by a conductive and sensorineural component. The conductive component was attributed to a loss of sensitivity produced by the excessive bony encroachment on the middle ear space and ossicles. The

sensorineural component was ascribed primarily to the entrapment of the 8th cranial nerve in the internal auditory canal. Bony overgrowth encroached on the internal auditory canal, compressing and damaging the 8th cranial nerve, restricting optimal nerve functioning. Sclerosteosis led to excessive bony overgrowth on the outer surface of the otic capsule, causing sclerosis of the periosteal layer of the cochlea, leaving the enchondral bony layer and endosteal layer unaffected. The cochlea was not primarily affected by sclerosteosis (Jahn, 1988; Schukecht, 1993).

Most subjects with sclerosteosis either made use of hearing aid amplification or a BAHA system. It would be important to evaluate the benefit of hearing aid amplification and BAHAs in sclerosteosis, as the middle ear and 8th cranial nerve were the main areas affected. The perceived outcomes of these systems should be surveyed to determine to what extent it improved quality of life in these subjects. Cochlear implants or ABIs might also be a rehabilitation option for alternative management, but the benefit of these devices had not yet been confirmed (Merkus, Free, Sanna, 2012; Sennaroglu & Ziyal, 2012)

4.3. Critical Assessment of Study Strengths and Limitations

The strengths and limitations of this research study were considered critically. This critical evaluation aided to direct future and continuing research. The strengths and limitations are discussed below.

4.3.1. Strengths of the study

Sclerosteosis is primarily restricted to Afrikaners of Dutch, French and German descent. The medical field was more aware of sclerosteosis, thus surgeons diagnose the disorder at birth. Extensive otolaryngological research on the history of sclerosteosis, the clinical presentation of sclerosteosis, radiographic and genetic studies had been conducted previously (Hamersma & Hofmeyr, 2009; Hofmeyr & Hamersma, 2004). There existed a dearth of research however with regard to the auditory profile and nonsurgical management of sclerosteosis, thus it was important to describe the hearing of individuals with sclerosteosis (Hofmeyr & Hamersma, 2004). Therefore this study aimed to provide information to determine the auditory profile of sclerosteosis.

This was the first study that described the function in sclerosteosis comprehensively, as no other data existed describing the auditory profile of sclerosteosis. Subjective testing (pure-tone air- and bone-conduction audiometry, speech audiometry) and objective testing (tympanometry, ABRs, DPOAEs, CT scans) promoted test reliability. The audiometric tests and CT scans were used to determine the auditory function in sclerosteosis. The study emphasised the audiometric configurations and test results to be expected in sclerosteosis. Sclerosteosis is a rare disorder, and there are only 36 subjects with diagnosed sclerosteosis in South Africa. This study was able to evaluate a third of the population living with sclerosteosis. Awareness of the possible surgical and non-surgical management of sclerosteosis was raised during the completion of this research project. The research determined a baseline for future and continuing research in sclerosteosis.

4.3.2. Limitations of the study

Although the research study addressed the research aim, there were still manifested limitations. Firstly, sclerosteosis is a rare disorder with only 36 known cases alive in South Africa. Some of the subjects contacted resided outside of the Gauteng region, therefore could not participate in the study, influencing the sample size. Eighteen subjects were contacted and only 10 could participate. It would have been valuable to have a bigger sample for more accurate generalisation. Secondly, alternative middle ear measures could have been used to evaluate middle ear function. The conventional tympanometry measurements conducted in this research study did not provide an accurate measure for identifying conductive pathology as compared with bone-conduction audiometry and the middle ear abnormalities visualised by CT scans. Thirdly, the researcher was unable to source the surgical history of all subjects. Limitations were encountered to the knowledge of previous middle ear, oval and round window, and internal auditory canal surgery. The study therefore was unable to determine the affect previous surgery had on the auditory function of sclerosteosis.

Finally, a cross-sectional research design was followed to conduct this study. The cross-sectional research design allowed a once-off audiological test-battery evaluation, which lasted approximately two hours. A longitudinal research design would have been preferred,

allowing frequent audiological test follow-ups. Results gathered from multiple sessions could provide information on the rate to which sclerosteosis progresses. Valuable information from the audiometric results and CT scans could guide surgical management and the timing thereof.

4.4. Future Research

This study described the auditory profile of subjects with sclerosteosis. Suggestions for future and continuing research are provided below.

Firstly, due to the false negative normal type A tympanograms recorded in 50% of ears in sclerosteosis, it would be recommended to explore high probe tone frequencies and wideband reflectance for susceptance and conductance component analysis in sclerosteosis. These recordings would provide more accurate information on the mass and stiffness of the middle ear system in sclerosteosis. Secondly, if the auditory nerve remained unharmed during the surgical decompression of the internal auditory canal in young children, future studies could document the possible management of hearing loss with cochlear implants. Thirdly, ABIs might be a possible option for the management of retro-cochlear involvement, but future investigations need to confirm the benefit of ABIs as a last resort treatment of sclerosteosis related auditory dysfunction. Fourthly, it could be valuable to determine the factors that aid in the successful management of conventional hearing aids versus BAHAs. Fifthly, a longitudinal study monitoring the effectiveness of intervention on a sample of at least 10 subjects would be valuable. Lastly, a longitudinal study documenting the journey of a sclerosteosis subject from onset of the disorder, surgical and non-surgical intervention over time would be valuable.

4.5. Conclusion

Subjects with sclerosteosis presented with anatomical abnormalities of the middle ear, oval and round windows of the cochlea and internal auditory canal. These abnormalities resulted in moderate to profound mixed hearing losses. Similarities in the audiometric findings, when compared to otosclerosis and other conditions characterised by abnormal bony growth were evident, although sclerosteosis related auditory dysfunction was typically more severe.

Abnormalities of the oval and round windows of the cochlea and internal auditory canal caused sensorineural involvement, evidenced by absent DPOAEs and absent or abnormal ABR findings. ABR and speech audiometry might assist in differentiating cases with significant involvement of the internal auditory canal. The progressive abnormal bony overgrowth, which is the hallmark of sclerosteosis, led to functional impairment at various levels in the auditory system. Current findings provided a comprehensive auditory profile for sclerosteosis and might be utilized alongside future research findings to direct criteria and audiological indications for surgical and audiological intervention.

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6. APPENDICES

APPENDIX A

Ethical Clearance - Faculty of Humanities, University of Pretoria



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Office of the Deputy Dean

10 August 2010

Dear Prof Swanepoel,

Project: An audiological profile and database of patients with
sclerosteosis: a longitudinal study
Researcher: J Potgieter
Supervisor: Prof DCD Swanepoel
Department: Communication Pathology
Reference number: 26029822


I am pleased to be able to tell you that the above application was **approved (with comments)** by the **Postgraduate Committee** on 20 July 2010 and by the **Ethics Committee** on 5 August 2010. Data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should the actual research depart significantly from the proposed research, it would be necessary to apply for a new research approval and ethical clearance.

The Committee requests you to convey this approval to the researcher.

We wish you success with the project.

Sincerely



Prof John Sharp
Chair: Postgraduate Committee &
Research Ethics Committee
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: john.sharp@up.ac.za

APPENDIX B

Procedure Information Letter and Informed Consent - Research Subjects



Date:

Researcher: Jenni-Mari Potgieter
Tel: 082 551 4938
E-mail: jenni-mari@lasik.co.za

TO WHOM IT MAY CONCERN:

Thank you for showing interest in this research project being conducted at the Department of Communication Pathology, University of Pretoria in collaboration with Dr Louis Hofmeyr and Prof H. Hamersma. The title of the research project is: ***An audiological profile and database of patients with sclerosteosis: A longitudinal study.***

This study will provide us with a description of hearing in individuals with sclerosteosis. The audiological data will assist to inform, direct and manage hearing loss in sclerosteosis. The study will involve Computed Topographic (CT) scans in order to document radiographic features. The study will also involve a series of diagnostic audiological tests of auditory functioning, which is completely harmless and non-invasive. Participation in the study is voluntary and you may withdraw at any time if you wish to. If you do participate the following procedures will apply to you:

- An otoscopic examination, followed by immittance measurements, will be carried out. Your outer ear canal, eardrum and middle ear functioning will be examined while you sit quietly. During immittance measures a small probe will be placed in your ear. These procedures do not require any response from you and will take approximately 5 minutes.
- You will then undergo a standard hearing evaluation (pure tone air and bone conduction behavioural audiometry and speech audiometry), where you are required to respond to the presence of a sound. You will also be asked to repeat a list of words as intensity decreases. This procedure takes approximately 20 minutes.
- An otoacoustic emission (OAE) test will be conducted. This procedure requires you to sit quietly and no response is required from you. During the OAE measurement a small probe will be placed in the ear. This procedure takes approximately 10 minutes.
- An auditory brainstem response (ABR) test will be conducted. Electrodes will be placed on your forehead and earlobes. Probes will be placed in your ears. You are required to lie quietly on a bed. This procedure does not require any response from you and will take approximately 40 minutes. Sleeping is encouraged.
- Muelmed Hospital will schedule a computed tomography (CT) scan.

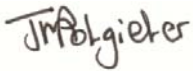
All the audiological test procedures are non-invasive and only the behavioural (pure tone air and bone conduction, speech audiometry) procedures require responses from you. It is also important to note that all information will be treated ***strictly confidential***. The results will be used for research purposes as part of a dissertation and possibly future articles and presentations. At no point in time

will any names or identifying information be made available. The data will be stored for archiving and research purposes at the University of Pretoria for at least 15 years.

By agreeing to participate in this study you acknowledge that future research using the acquired data may be conducted at a later stage. A copy of your results will be made available to you, should you request it. **You are free to withdraw from the study at anytime** without any negative consequences.

Should you require any further information, you are welcome to contact us.

Sincerely,



Jenni-Mari Potgieter

Researcher



Prof. De Wet Swanepoel
Supervisor

Dr. Maggi Soer
ACTING HEAD OF DEPARTMENT: Department of Communication Pathology

University of Pretoria
Department Communication Pathology: Audiology

INFORMED CONSENT FORM

An audiological profile and database of patients with sclerosteosis: A longitudinal study.

Please complete the following:

Surname: _____

Name: _____

Age: _____

I, hereby agree to participate in this project and acknowledge that the data may be used for research purposes. I am aware that I can withdraw from this project, at any time, should I want to.

Signature

Date

APPENDIX C

Information Letter - Prof. L.M. Hofmeyr and Prof. H. Hamersma

Informed Consent - Dr L.M. Hofmeyr



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Communication Pathology

3 April 2010

TO: Prof. L. M. Hofmeyr, Prof. H. Hamersma

RE: DESCRIPTIVE CROSS-SECTIONAL STUDY OF AN AUDIOLOGICAL PROFILE OF INDIVIDUALS WITH SCLEROSTEOSIS

Herewith we kindly request permission to conduct collaborative research with you to describe the auditory profile, clinical and radiographic features of individuals with sclerosteosis. The research study will consist of two components. The first component is a retrospective study, which involves the review of patient files. We request permission to review the patient medical records to collect pre-operative and post-operative data. The second component is a prospective study. Audiological, clinical and radiographic examinations will be conducted for each participant to collect delayed post-operative data. We request permission to contact the patients involved in the retrospective study to participate in the prospective component of the study. It is hoped that the processing of this data will provide valuable information to inform, direct and monitor management in new cases of sclerosteosis.

Patients' participation will be voluntary based on informed consent, which will be provided as a letter to each patient. All data will be treated confidential and codes will be assigned to each patient to ensure all identifying information is kept anonymous. Processed data will be used towards completion of a thesis towards the degree M.Communication Pathology for Ms Jenni-Mari Potgieter and may also be used for teaching purposes or may be presented at conferences or published in article format. Data will be stored for a minimum of 15 years according to University of Pretoria regulations. A research proposal will be submitted to the ethics committee of our Faculty at the University of Pretoria.

If you require any information or have additional queries, please do not hesitate to contact us at 012 420 2304 (Prof. De Wet Swanepoel) and 082 551 4938 (Ms. Jenni-Mari Potgieter).

We are grateful for your time and appreciate your assistance.

Request authorized / rejected.



Prof. L.M. Hofmeyr

PROF L M HOFMEYR
MBChB (Pret) MMED ENT (Pret)
ENT SPECIALIST (Otolology & Neur-Otology)
MP 0408042 / Pr Nr 030 000 0041637

APPENDIX D

Information Letter - Dr. A.A.S. Burger, Department of Radiology,

Muelmed Mediclinic

Informed Consent - Dr. A.A.S. Burger



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Communication Pathology

April 2010

TO: DRS. DE BEER, DE JAGER RADIOLOGISTS

ATTENTION: DR. ANDRE BURGER

RE: DESCRIPTIVE CROSS-SECTIONAL STUDY OF AN AUDIOLOGICAL PROFILE OF INDIVIDUALS WITH SCLEROSTEOSIS

Herewith we kindly request permission to conduct collaborative research with Muelmed Hospital to describe the radiographic features of individuals with sclerosteosis. It is hoped that the processing of this data will provide valuable information to inform, direct and monitor management in new cases of sclerosteosis and also to establish a database.

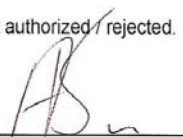
We kindly request your cooperation to assist us in the conduction of High Resolution Computerized Tomography (CT) scans without contrast of the temporal bones. We would appreciate permission to conduct the CT scans for 20 – 25 patients without the involvement of any financial liabilities. Sighting your names in any article to be published will repay your contribution towards the research study.

Patients' participation will be voluntary based on informed consent, which will be provided as a letter to each patient. All data will be treated confidential and codes will be assigned to each patient to ensure all identifying information is kept anonymous. Processed data will be used towards completion of a thesis towards the degree M.Communication Pathology for Ms Jenni-Mari Potgieter and may also be used for teaching purposes or may be presented at conferences or published in article format. Data will be stored for a minimum of 15 years according to University of Pretoria regulations. A research proposal will be submitted to the ethics committee of our Faculty at the University of Pretoria.

If you require any information or have additional queries, please do not hesitate to contact us at 082 339 4926 (Dr. Louis Hofmeyr), 012 420 2304 (Prof. De Wet Swanepoel) and 082 551 4938 (Ms. Jenni-Mari Potgieter).

We are grateful for your time and appreciate your assistance.

Request authorized / rejected.



Dr. André Burger

To God the Glory!