

Osteogenesis Imperfecta and Hearing Loss : A South African Perspective

A Research report submitted to The University of The Witwatersrand in partial fulfilment of the requirements of the Master of Medicine degree,
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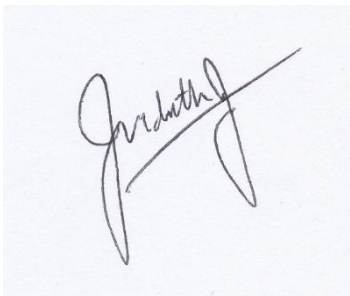
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Otorhinolaryngology

FACULTY OF HEALTH SCIENCES

Declaration

I, Judith Kamala Joseph, hereby declare that this research is my own work. I am submitting this research report in the submissible format with my protocol and extended literature review for the degree Master of Medicine in the branch of Otorhinolaryngology at the University of Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other university.

A handwritten signature in black ink, appearing to read 'Judith Kamala Joseph', is written over a light blue rectangular background.

On 26th day of September 2022

Acknowledgements

I would like to thank God for His gracious love and for all His blessings.

I would like to thank my husband and my son for their patience and support.

I would like to thank Prof Shivesh Maharaj for his expert mentorship, patience and guidance.

I would like to acknowledge all the patients who participated in this study without whom all this would not have been possible.

I would like to thank all the staff at the Metabolic Bone Clinic and the Department of Audiology , Chris Hani Baragwanath Academic Hospital.

ABSTRACT

Osteogenesis imperfecta (OI) is a genetic disorder that affects the synthesis of collagen in the body. It is also known as 'Brittle Bone Disease'. It is heterogeneous in its clinical presentation. The commonest presentation is a history of frequent fractures, joint deformities and blue sclera. Secondary deformities of the extremities, spine, skull as well as short stature frequently observed.

Hearing loss has been well documented to occur in OI. It is most commonly seen in types I, II and III. Hearing loss forms part of the diagnostic criteria for these types. Depending on the study, the prevalence of hearing loss in children with OI is between 6.7 % and 77.3%

The estimated prevalence of OI is 1 in 20000. In South Africa, the commonest type of OI was found to be Type III. The prevalence of OI Type III has been estimated to be between 1:125000 and 1:200000. Hearing loss is a common feature of OI Type III. Studies such as this will contribute to the body of knowledge of OI and will in future help researchers identify the cause of the hearing loss.

METHODS

This study was a prospective cross-sectional study. Ethics Approval was obtained from the University of Witwatersrand Ethics committee (Ethics number M190975). Children with OI attending the Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital were the target group. The patients and their parents or guardians were recruited at the clinic after a consent and or an assent was obtained. An otoscopy followed by tympanometry and a hearing screen based on the age of the patient was done.

DPOAE (Distortion Product Oto-Acoustic Emission) tests were also done as a screening test to confirm the pure tone audiogram findings. The results were given to the patients and their parents/ guardians immediately.

RESULTS

The paediatric patients with OI who consented to take part in the study had their hearing screen done at the Audiology Department at Chris Hani Baragwanath Academic Hospital. All of the children were found to have normal hearing. On tympanometry, all except 2 were found to have type A curves in bilaterally. Two patients had a type As curve in one ear with an A curve on the other side.

CONCLUSION

Hearing loss in OI forms part of the diagnostic criteria for certain types of this genetic disorder. Hearing loss in the paediatric patients does not seem to be as prevalent as previously thought. All the patients involved in the study received the bisphosphonate therapy (Zoledronic acid) for OI. This may possibly cause a delay in the onset of hearing loss but long term follow-up studies and bigger sample sizes will be required to prove this hypothesis.

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Abbreviations

OI	Osteogenesis imperfecta
DPOAE	Distortion Product Oto-Acoustic Emission
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital

Introduction

Osteogenesis imperfecta (OI) is an inherited bone and connective tissue disorder associated with the lifelong occurrence of frequent fractures. The estimated prevalence of OI is 1 in 20,000 (1). It is markedly heterogenous in its clinical presentation (table 1). The main defect in this disease is in the synthesis of type 1 collagen. Secondary deformities of the extremities, spine, skull as well short stature are commonly observed (2). Hearing loss has also been documented to occur in OI. The prevalence of hearing loss has been estimated to be about 62% (3). The hearing loss varies with the type of OI and is most common in Type I, and is rarely reported in Type IV OI (4,3).

Table 1: Types of Osteogenesis Imperfecta

Type	Inheritance	Clinical Features
I	AD	Mild, blue sclerae, fractures with little or no deformity, hearing loss, dentinogenous imperfecta
II	AD, AR	Lethal, pulmonary insufficiency, beaded ribs, rhizomelic short stature, hearing loss
III	AD, AR	Progressive deforming, intrauterine fractures, deformed limbs, scoliosis, white or blue sclerae, hearing loss, dentinogenous imperfecta
IV	AD	Moderately severe, limb deformity, sclerae blue early and lightens with age, scoliosis
V	AD	Variable phenotype like IV, hyperplastic callus, dislocated radial head, calcified interosseous membrane
VI	Unknown	More fractures than IV, mineralization defect on biopsy, vertebral fractures, no dentinogenous imperfecta
VII	AD	Congenital fractures, white sclerae, severe rhizomelia

Hearing loss is most commonly seen in OI types I, II and III (4). The type of hearing loss was found to vary. A study done at Johns Hopkins by Pillion and Shapiro (3) showed that the younger age group most commonly had conductive hearing loss and in the older age groups, the hearing loss was sensorineural, conductive or mixed. They found that conductive hearing loss occurred in 21% and sensorineural and mixed hearing loss occurred in 41% of the patients surveyed. In OI, the hearing loss is predominantly conductive in children (5,7).

In South Africa, the commonest type of OI was found to be Type III (8). The prevalence of OI Type III has been estimated to be between 1:125000 and 1:200000 (6). Hearing loss is a common feature of OI Type III (4).

The purpose of this study is to determine the prevalence of hearing loss in patients with OI. It has been well established that hearing loss forms a part of the spectrum of clinical features seen in OI. It has also been proven that there is a high prevalence of hearing loss in OI (10). Osteogenesis imperfecta has been well documented in South Africa (8,9).

Genetic studies and various treatment modalities have also been documented and published (8,9). However, a hearing screen of these patients has never been done in Africa.

At present, no hearing screens have been routinely done for patients with OI. This needs to be addressed and this study can help facilitate this. The data obtained may be useful to clinicians and other allied health professionals involved in the care of OI patients. The data obtained may be valuable to other researchers and to future research conducted by the University.

These patients are already being seen at their respective orthopaedic clinics and hence testing and follow up at the Audiology clinic will not be inconvenient for them.

Literature Review

Osteogenesis Imperfecta (OI) has been well documented and studied in South Africa. Most of the focus of research and study has till date been on the management of fractures which characterise this condition. Genetic studies have been done in OI Type III which is the most common variant found in South Africa. Vorster et al (8) found that FKBP10 mutation occurred in 45.1 % (41) of the 91 children with OI Type III. All of the patients were of the local African population. Oduah et al (2) in their article on the management of Osteogenesis Imperfecta at CHBH also found that the majority (48.7%) of their OI patients were Type III. They also noted that the OI Type III patients had the highest number of fractures on average.

The genes most commonly associated with OI are COL1A1 and COL1A2 which are in turn associated with collagen synthesis. Many other genes including the mutation FKBP10 have been identified and added to the classification of OI. (11) Many of the newly identified variants are recessive or X-linked in their inheritance.

Hearing loss forms a part of the diagnostic criteria for OI and has been well documented. Hearing loss is more frequently seen in the adult population but is also seen in the paediatric population. Kuurila et al (5) found in their study done in 2000, that only 6.7 % (3 out of 60) had hearing loss. Two of the patients had bilateral conductive hearing loss and one had bilateral severe sensorineural hearing loss. However, a previous study by Pedersen (7) found conductive hearing loss in 22% of the patients in the 4-9 year age group. In addition, 28% of the patients in the 10-19 years group had mainly conductive hearing loss. In this Danish study, a total of 201 patients in the paediatric group were screened. The classification of hearing loss as a pure tone below 15 dB in a single or more frequencies could have contributed to the prevalence of hearing loss.

A recent study done in Brazil demonstrated a higher hearing loss among adults than in children. (12) The study looked at 3 different groups, children (0-10 years), adolescents (10-19 years) and adults (20 years and older). In the children's group, 81.3% had normal hearing and in the adolescent group, 65% had normal hearing. Among the adult patients with OI, 54.4% had normal hearing. In the children and adolescent groups, the hearing loss was predominantly conductive in nature. In the adult group, the hearing loss was either sensorineural or mixed. They also found that the OI Type I patients had normal hearing whereas the patients with OI Type IV had a higher prevalence of hearing loss. This is in contravention of what is commonly reported in literature with OI Type I having a higher prevalence of hearing loss and OI Type IV rarely having hearing loss.

A multicentric North American study published in 2020 demonstrated a marked increase in hearing loss in female patients with OI. (13) The total prevalence was 28.3% with a higher prevalence of sensorineural hearing loss in female patients. They also found that hearing loss was predominantly in the OI Type I group and increased with age.

Hearing loss in OI has been postulated to be ossicular in origin. Stapedotomy has been used in the treatment of conductive hearing loss in OI. In a study done in Poland, the intra-operative findings during stapedotomy were noted. The commonest pathology encountered was stapes footplate fixation. Far less commonly seen was the fixation of the malleus and incus in the epitympanum. The patients with OI Type III were most likely to have fractures and also seem to present with the highest number of ossicular malformations. They also had the highest number of re-stapedotomy procedures done. The prostheses were more likely to be displaced by bony deposits with a higher refixation rates. They also found that OI patients were more likely to have their stapedotomy procedures complicated by bleeding.(14)

Ting et al (15) found that none of the patients who received bisphosphonates had significant hearing loss. Thirty-six paediatric patients with OI were screened and none were found to have hearing loss. All of the patients were being treated with bisphosphonates. The previous prevalence studies done in children with hearing loss did not mention if the children were being treated with bisphosphonates or not. This is the first study to comment on specifically children who had received bisphosphonates.

Bisphosphonates have been shown to decrease the incidence of fractures in metabolic bone disease and forms part of the treatment for OI. The side effect profile of this group of drugs has been extensively studied. A review of the adverse effects of bisphosphonates by Papapetrou (16) showed that hearing loss has not been reported to occur as a result of treatment with this drug. A study done by in the Harvard Medical School looked at the effect of bisphosphonates in improving cochlear function. The study demonstrated the regenerative effect of bisphosphonates on synapses in the cochlea in mice. (17)

Study Aim

The aim of the study is to determine the prevalence of hearing loss and to classify the type of hearing loss in patients with osteogenesis imperfecta seen at the Orthopaedics Clinic at CHBAH and CMJAH.

Study Objectives

1. To determine the presence or absence of hearing loss in patients with osteogenesis imperfecta.
2. To determine the types of hearing loss, if present.
3. To compare the hearing loss patterns in the two different age groups:
Paediatric (0 – 18 yrs) and Adult (> 18 yrs).

Methodology

Study Design

Cross-sectional study

Site of Study

CHBAH and CMJAH.

Study Population

All patients with Osteogenesis Imperfecta registered at the Specialist Orthopaedic Clinic at CMJAH and CHBAH between Feb 2020 to April 2021

Inclusion Criteria

All patients being seen at the Specialist Orthopaedic Clinics at CMJAH and CHBAH and who have consented to participate in this study. In the case of children, the parental (or guardian) consent will be obtained along with the child's assent. All the consents and assents will be obtained by the researcher along with the help of a trained translator if required.

Exclusion criteria

1. Patients for whom a hearing test cannot be performed.
2. Patients who have not given consent. In the case of children, the parental (or guardian) consent has not been given and the child's assent has not been obtained.
3. Patients with chronic otitis media.

Data Collection

The objectives of the study and the procedure will be explained to the patients and informed consent will be obtained from the patients or their guardians. Otoscopy will be done for all the patients. The otoscopy will be done by the researcher. The patients will then be sent for audiological assessments.

The sample size is calculated to be 85.24 with a CI of 95%. The aim is to include 85 patients.

The following tests will be administered to the study participants based on their age groups. The tests will be done under standard conditions in a soundproof room in the Departments of Audiology at CHBAH and CMJAH. All tests will be performed on

standardised machines that are regularly calibrated. The tests will be administered by audiologists who have been trained in these standardised tests.

Age group (0 - 1 yr)

- Visual Re-enforcement Audiometry (in suitable infants)
- Distortion Product Otoacoustic Emission (DPOAE)
- Automated Auditory Brainstem Response (AABR)
- Tympanometry (1000 Hz)

Age group (1 – 5 yrs)

- Play Audiometry
- AABR
- Tympanometry

Above 5 yrs, including adults

- Conventional Audiometry (Pure Tones)
- Tympanometry
- DPOAE
- Acoustic Reflexes testing
- Automated Auditory Brainstem Response (AABR) if required

The machines used are Interacoustic ac-40, Hass Audiometer and Medtronic Otoacoustic machines. They are all calibrated on a regular basis.

The data will be collected by the researcher from the patient's audiograms. The type of hearing loss will be determined by tympanometry and classified. (Table 2)

Table 2: Classification of Hearing Loss

dB	Hearing Loss
< 25	No Hearing Loss
26 – 40	Mild
41 – 55	Moderate
56 – 70	Moderately Severe
71 – 90	Severe
>90	Profound

Ethics

Patients will be enrolled in the study only when informed consent has been obtained. In the case of children (under 18 yrs) , parental (or guardian) consent will be obtained along with the child's assent. Patient confidentiality will be respected at all times. Personal data will not be collected and only relevant demographic data will be collected. Permission to conduct the study will be obtained from the Heads of the Department of Orthopaedics at CMJAH and CHBH. Permission will also be obtained from the Heads of Department of Audiology at CMJAH and CHBH.

Prior approval to conduct the study will be obtained from the Human Research Ethics Committee of the University of Witwatersrand.

Data Analysis

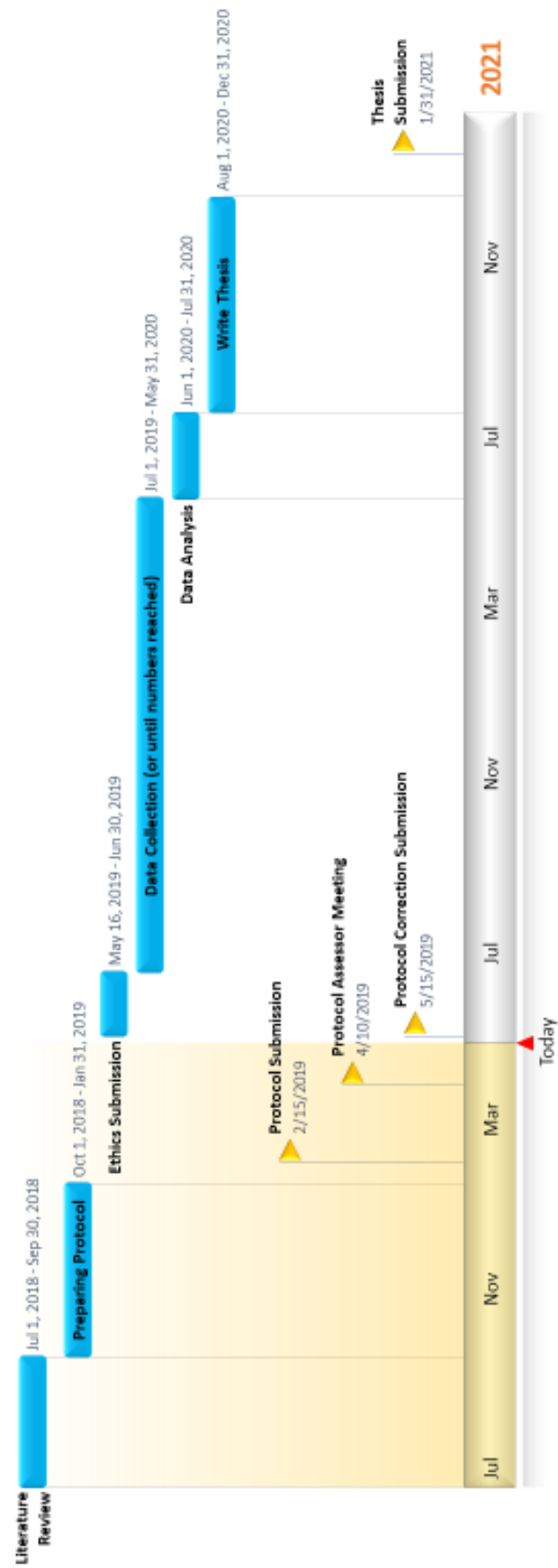
All data will be captured from the audiograms and entered into an electronic spreadsheet. The hearing loss, if present will be classified according to the current Audiological Association of South Africa guidelines.

The prevalence of hearing loss in patients with Osteogenesis Imperfecta in the two age groups will be calculated. The types of hearing loss (Conductive vs. Sensorineural) will

be tabulated and classified. The prevalence risk ratio will be calculated. A Pearson's chi-squared test will be performed to compare the expected and observed results.

The data collected will then be compared to data obtained from similar studies done in other parts of the world. The prevalence of hearing loss in childhood and in adults will be compared. OI being primarily a genetic disease, could have a different disease profile Africa. The hearing loss could be of a different type or of a different severity (greater or lesser). This data may help clinicians formulate a more comprehensive treatment plan for patients.

Timing



Funding

None requested. Any extraneous expenses will be borne by the researcher.

Limitations

The study will be limited by time due to the fact that only 3 patients can be tested on the allotted days and the tests are time-consuming. The patients come from all over the country to the orthopaedic clinic at CHBAH and hence distance is also a limitation.

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DATA COLLECTION SHEET

Patient Number							
Age							
Sex	male		female				
Demographics	Black	White		Indian	Coloured		
Osteogenesis Imperfecta type	I	II		III	IV		
Hearing	Normal	Decreased					
RIGHT EAR- Otoscopy- Tympanic Membrane	Normal		Dull		Retracted		
Tympanometry	A	B		C		As/Ad	
Type of Hearing Loss	Conductive		Sensorineural		Mixed		
Hearing Loss (db)	Mild (26-40)		Moderate (41-55)		Moderately severe(56-70)		
	Severe (71-90)			Profound (>90)			
LEFT EAR- Otoscopy- Tympanic Membrane	Normal		Dull		Retracted		
Tympanometry	A	B		C		As/Ad	
Type of Hearing Loss	Conductive		Sensorineural		Mixed		
Hearing Loss (db)	Mild (26-40)		Moderate (41-55)		Moderately severe(56-70)		
	Severe (71-90)			Profound (>90)			

CONSENT FORM

Name of the Study - Osteogenesis Imperfecta and Hearing Loss :
a South African Perspective.

I , _____ (Parent of _____) give consent to my /my
child's participation in the study explained to me by the researcher. I am willing to
undergo / have my child undergo the hearing tests. I am aware that the results of
the tests will be used in a study and I give consent to the same. I understand that my
name (my child's name) and personal details will be kept confidential. I am aware that
there is no direct benefit or incentive to participate in this study.

Signed _____

Date-

Witness 1. _____

Witness 2. _____

ASSENT FORM

Name of the study – Osteogenesis Imperfecta and Hearing Loss

A South African Perspective

I understand that I have been asked to participate in a study about Osteogenesis Imperfecta and Hearing loss. I understand that I will be asked to take some tests to check my hearing. I understand that I do not have to participate.

The tests will be done at CHBAH / CMJAH at the Audiology Department.

When I sign my name, it means that I have decided to participate in this study. The researcher (Dr. Joseph) has explained the process to me and I do not have any more questions.

Name: _____

Signature: _____

Date: _____

Witness: _____

Witness: _____

Chapter 2 – Submissible Article

Osteogenesis imperfecta and hearing loss in the paediatric population

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Abstract

Background: Osteogenesis imperfecta (OI) is a genetic disorder affecting the synthesis of collagen in the body. It is also known as 'Brittle Bone Disease'. It is heterogenous in its clinical presentation. The commonest presentation is a history of frequent fractures, joint deformities and blue sclera. Secondary deformities of the extremities, spine, skull as well short stature observed frequently. Hearing loss has been well documented to occur in OI. It is most commonly seen in types I, II and III. Hearing loss forms part of the diagnostic criteria for these types. Depending on the study, the prevalence of hearing loss in children with OI is between 6.7% and 77.3%. The estimated prevalence of OI is 1 in 20000.

Objectives: In South Africa, the commonest type of OI was found to be Type III. The prevalence of OI Type III has been estimated to be between 1:125000 and 1:200000. Hearing loss is a common feature of OI Type III. Methods: This study was a prospective cross-sectional study. Ethics Approval was obtained from the University of Witwatersrand Ethics committee (Ethics number M190975). Children with OI attending the Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital were the target group. The

patients and their parents or guardians were recruited at the clinic after a consent and or an assent was obtained. An otoscopy followed by tympanometry and a hearing screen based on the age of the patient was done. To confirm the results of the hearing tests, Distortion Product Otoacoustic Emission (DPOAE) tests were performed. The results were given to the patients and their parents/guardians immediately.

Results: The paediatric patients with OI who consented to take part in the study had their hearing screen done at the Audiology Department at Chris Hani Baragwanath Academic Hospital. All of the children were found to have normal hearing. On tympanometry, all except 2 were found to have type A curves bilaterally. Two patients had a type As curve in one ear with an A curve on the other side.

Conclusion: Hearing loss in Osteogenesis Imperfecta forms part of the diagnostic criteria for certain types of this genetic disorder. Hearing loss in the paediatric patients does not seem to be as prevalent as previously thought. All the patients involved in the study received the bisphosphonate therapy (Zoledronic acid) for OI. This may possibly cause a delay in the onset of hearing loss but long term follow-up studies and bigger sample sizes will be required to prove this hypothesis

1. Introduction

Osteogenesis imperfecta is an inherited Mendelian disorder of bone and connective tissue. The main defect in this condition is the synthesis of type 1 collagen which can be a qualitative defect with a smaller amount of collagen being produced or a quantitative defect with abnormal collagen being produced. The commonest presentation is a history of frequent fractures, joint deformities and blue sclera [1]. The disease is heterogenous in its presentation with secondary deformities of the extremities, spine, skull as well as short stature being seen frequently [2]. The Silvers Classification is used to define the various types of Osteogenesis Imperfecta [3]. The types I– IV are autosomal dominant but with the discovery of autosomal recessive types, the classification had been extended to include up to type XVI [1]. The autosomal dominant types account for 85–90% of the total number of cases of OI [4]. In these 4 types, mutations in the COL1A1 and COL1A2 genes cause the defective formation of type 1 collagen. Hearing loss forms

a part of the diagnostic criteria for certain types of OI. Hearing loss is commonest in type I but is also documented in types II and III [4]. Globally, 73–92% of all patients with OI type I have hearing loss [5]. The overall prevalence of hearing loss is estimated to be 62% [6]. The prevalence of hearing loss increases with the age of the patient and this is especially seen in OI type 1 [7]. A recent prevalence study done in the United States reported a prevalence of 28% [7]. The worldwide prevalence of the condition has been estimated to be 1 in 20000 [1]. In South Africa, the commonest type of OI was found to be Type III [8]. Its prevalence has been estimated to be between 1 in 125000 to 1 in 200000 [6]. Molecular screening study of South African patients with OI type 3 showed that 45.1% of the patients had a FKBP10 mutation. This variant is inherited in an autosomal recessive pattern [9]. These patients present with severe deformities, spinal malalignment and numerous fractures. When they also present with congenital contractures, it is designated as Bruck syndrome [10]. The hearing loss that these patients typically present with is heterogenous. There is no correlation documented between the severity of the disease and the severity of the hearing loss. It starts as a conductive hearing loss primarily in the younger age group and progresses to sensorineural hearing loss [11]. When hearing loss presents as a conductive loss, the area in the temporal bone most commonly involved is the stapes footplate causing fixation of the stapes footplate. It can sometimes be accompanied by the obliteration of the oval window niche. The sensorineural hearing loss has been postulated to be due to the abnormal temporal and the labyrinth itself [12]. Among the patients with hearing loss, the type of hearing loss was found to vary. A study done at Johns Hopkins Hospital showed that the younger age group most commonly had conductive hearing loss and in the older age groups, the hearing loss can be sensorineural, conductive or mixed [6]. They found that conductive hearing loss occurred in 21% and sensorineural and mixed hearing loss occurred in 41% of the patients surveyed. The hearing loss is predominantly conductive in children [13]. The prevalence of hearing loss in children with OI varies from 6.7 to 77.3% [5]

2. Methods

The patients involved with the study received treatment at the Paediatric Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa. The patients came from all over the country to receive intravenous bisphosphonates. Informed consent from the parents and guardians and assent in the case of older children was obtained. The hearing tests were conducted in the Audiology Department by senior audiologists. Otoscopic examination of the tympanic membrane was performed. The patients underwent a pure tone audiogram and an impedance tympanometry. The thresholds for 500 Hz, 1 kHz, 1.5 kHz, 2 kHz and 4 kHz frequencies were recorded. The pure tone average was calculated from the average of the thresholds of 500 Hz, 1 kHz and 2 kHz. Normal hearing was defined as the pure tone thresholds for 500 Hz, 1 kHz, 1.5 kHz, 2 kHz being at 20 dB or above. Distortion Product Otoacoustic Emission (DPOAE) tests were also done for all the patients.

2.1. Patient selection

2.1.1. Inclusion criteria All patients being seen at the Specialist Orthopaedic Clinics at CHBAH and who have consented to participate in this study. In the case of children, the parental (or guardian) consent had been obtained along with the child's assent. All the consents and assents were obtained by the researcher along with the help of a trained translator if required. The patients were all in the paediatric age group (<18 yrs of age) with a diagnosis of Osteogenesis Imperfecta.

2.1.2. Exclusion criteria

1. Patients for whom a hearing test could not be performed.
 2. Patients for whom consents could not be obtained.
- 2.2. Patients with chronic otitis media

2.2.1. Ethical considerations

As this was an observational study, there was no intervention involved in the study. It was of benefit to the children to have a hearing test due to the nature of the disease.

Ethics Approval was obtained from the University of Witwatersrand Ethics committee (Ethics number M190975).

3. Results

The study was conducted from December 2019 to February 2021. A total of 22 patients were screened ; 13 girls (59.1%) and 9 boys (40.9%). The youngest patient was 11 months old with the oldest being 15 yrs. The mean age was 7.57 yrs. The median age for the group was 7 yrs. Eleven of the patients had OI type III (50%), 3 had OI type IV (13.6%) and 8 had unclassified OI (36.4%) (Table 2). Included in the patient group were 6 year old fraternal twins with OI type III. Two of the boys had Bruck syndrome (a variant of OI type III). One was 15 years old and the other was 11 years old. All of the patients had normal hearing.

Impedance tympanometry was found to be type A bilaterally for 20 patients. Two patients had unilateral Type As curves with a Type A curve on the opposite side. In total, 42 ears had type A curves with 2 ears having Type As curves. None had type B or C curves.

4. Discussion

The total number of patients screened was 22. Due to the onset of the COVID-19 pandemic, the patient numbers were severely restricted. The patient's access to the orthopaedic clinic was also severely restricted. Hearing screening test were cancelled for a large part of 2020 and hence the lower than expected number of patients. Of those screened, the majority of the patients had OI type III which is in keeping with previously published literature [2,8]. Only 4 patients had OI type IV and 8 were unclassified. These patients presented with a mixture of characteristics of both type III and IV and hence were considered unclassified. Two patients had Bruck syndrome which is a variant of OI type III. The binomial probability was calculated to be 0.22 which is well in keeping with a prevalence of 6.7% [13].

Hearing loss has been well documented to form a part of the disease profile of OI. However, not all the different types of OI have hearing loss. The prevalence of hearing loss varies widely between 6.7% and 77.3% [5,12]. In these studies, the use of bisphosphonates had not been mentioned. Because of the high prevalence of hearing loss in the disease, regular hearing screening had in the past been advocated for patients with OI. The prevalence has been found to increase with age [7].

In this study we found that none of the patients with OI had hearing loss. The binomial probability was calculated to be 0.22. Kuurila et al [13], in their study found that only 6.7% had hearing loss. This is similar to the prevalence found in this study. In the impedance tympanometry tests, only two patients were found to have As curve in one ear each. (Table 1) This could possibly be due to a resolving otitis media. However, for both patients the pure tone audiometry was well within the normal hearing thresholds. Conductive hearing loss has been described to occur in childhood in OI. Sensorineural hearing loss has been documented to start in the second decade and is not commonly seen in the first decade [6,13].

All the patients in this study had been on treatment with zoledronic acid (also known as zoledronate) which is a bisphosphonate. This treatment may have had an influence on the study outcome. Ting et al [14] found that none of the patients who received bisphosphonates had significant hearing loss. A literature review of OI and hearing loss confirmed that Ting et al. reported a significantly lower prevalence of hearing loss than any other prevalence study [15]. This result is in keeping with what we found in our patient group. Bisphosphonates have formed the figurative backbone of treatment of OI.

Bisphosphonates improve the ossification of bones in children with OI and reduce the incidence of fractures. They have not been described to cause hearing loss.

Bisphosphonates have been proven to stabilise the sensorineural hearing loss in cochlear otosclerosis [16]. The improved ossification could possibly decrease or a delay in the fracture of the crurae of the stapes and improved ossification of the temporal bone. This is in keeping with the hearing loss being conductive initially and then becoming a mixed or sensorineural hearing loss [7].

Hence we tentatively postulate that the bisphosphonate treatment, in addition to strengthening the bones, delayed the onset of hearing loss in children with OI. Hearing loss in paediatric OI patients appears to be much lower than previously reported. Follow up studies with bigger sample sizes are required. An interventional trial is underway in New York at the Hospital for Special Surgery. The effect of bisphosphonates on hearing loss in OI patients is being observed. We look forward to the results from this clinical trial [17].

5. Conclusion

Osteogenesis imperfecta is rare debilitating disorder of the bones. Hearing loss forms a prominent part of the symptom profile of this disorder. The mainstay of treatment for OI is bisphosphonate therapy. Hearing loss in the paediatric OI group does not seem to be as prevalent in our centre as previously reported in literature. One possible explanation for this could be that the treatment with Zolendronic acid has mitigated or delayed the onset of hearing loss. However, the main limitation of this study is the small sample size. Prospective observational studies with larger and case-control studies will be able to conclusively prove this hypothesis.

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Declaration of competing interest

The authors hereby declare that they have no conflict of interest.

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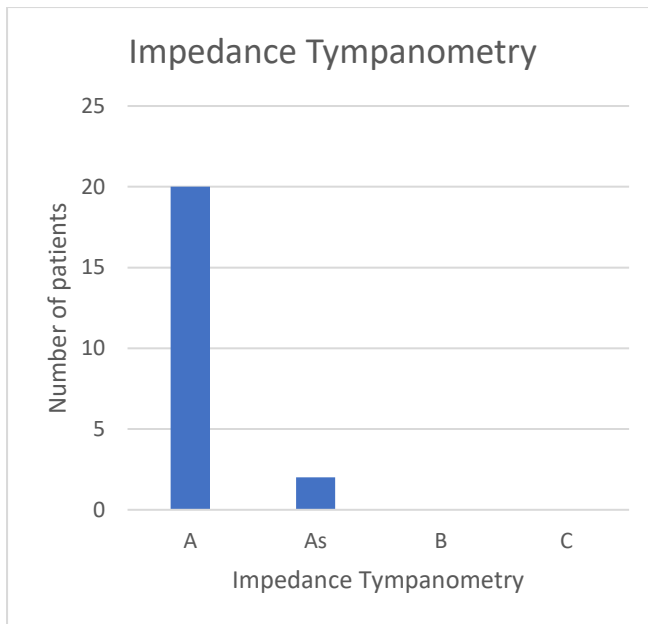


Table 1

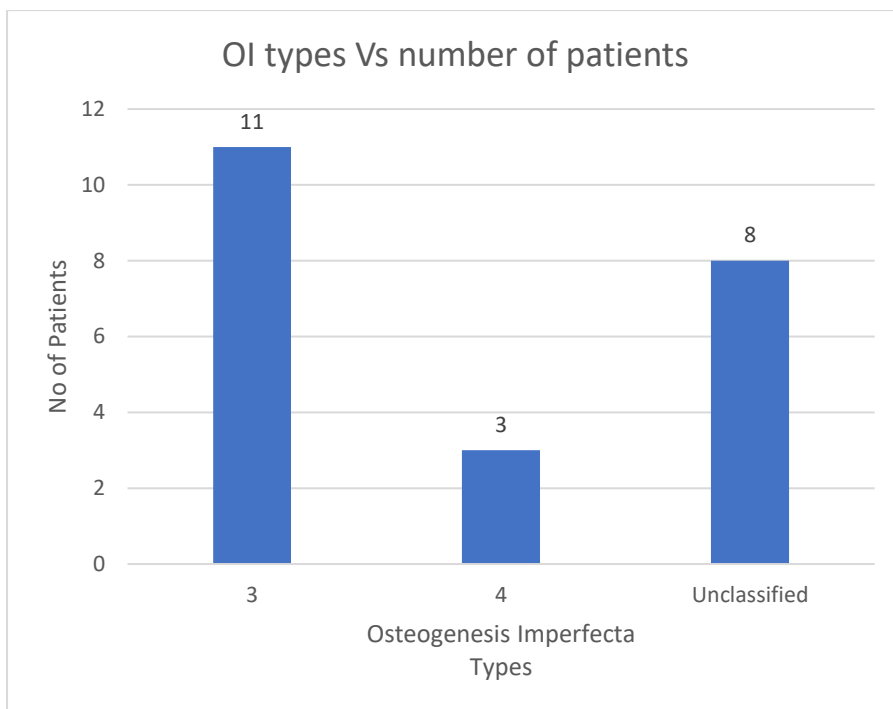


Table 2