



Osteogenesis Imperfecta and hearing loss in the paediatric population

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ABSTRACT

Background: Osteogenesis Imperfecta 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 Osteogenesis Imperfecta. 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 Osteogenesis imperfecta is between 6.7% and 77.3%. The estimated prevalence of Osteogenesis Imperfecta is 1 in 20000.

Objectives: In South Africa, the commonest type of Osteogenesis Imperfecta 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 Osteogenesis Imperfecta 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. DPEOAEs 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 Osteogenesis Imperfecta 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 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 were receiving 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 Silence 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

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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 Osteogenesis Imperfecta was found to be Type III [8]. It's 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 a 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]. (7) 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 by Pillion and Shapiro 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 Osteogenesis imperfecta varies from 6.7 to 77.3% [5].

2. Methods

The patients involved with the study received treatment the Paediatric Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital 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 K being at 20 db or above. DPOAEs 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 CMJAH and 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. There was a total of 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%) (Fig. 2). Included in the patient group were 6 year old fraternal twins with OI type 3. Two of the boys had Bruck syndrome (a variant of OI type 3). 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. The majority of the patients had OI type 3 which is in keeping with previously published literature [2,8]. Only 4 patients had OI type 4 and 8 were unclassified. These patients presented with a mixture of characteristics of both type 3 and 4 and hence were considered unclassified. Two patients had Bruck syndrome which is a variant of OI type 3. The binomial probability was calculated to be 0.2175 which is well in keeping with a prevalence of

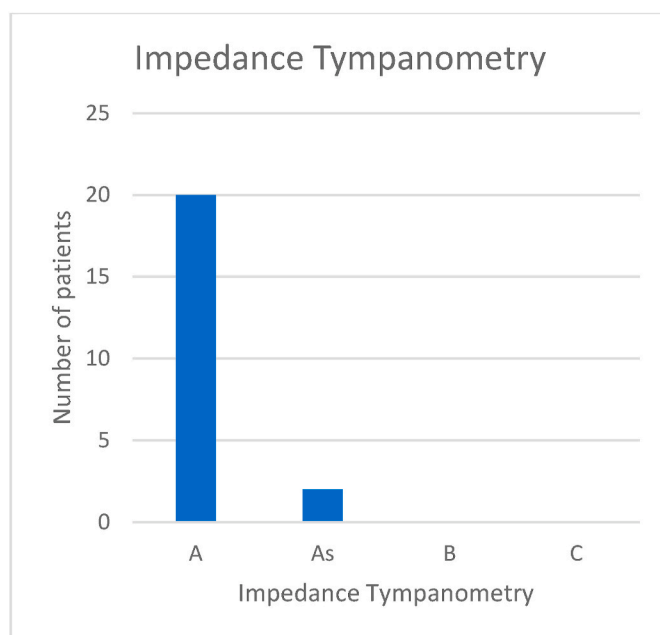


Fig. 1. Tympanometry of patients with OI.

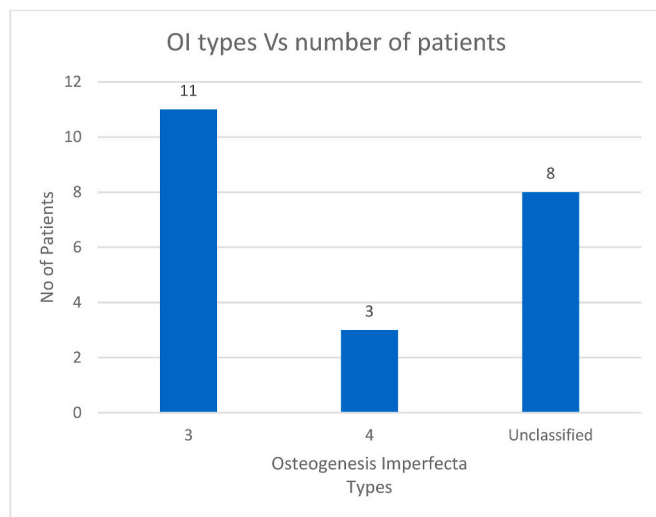


Fig. 2. Subtypes of OI.

6.7% [13].

Hearing loss has been well documented to form a part of the disease profile of Osteogenesis imperfecta. However, not all the different types of Osteogenesis imperfecta 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].

Kuurila et al., in their study found that only 6.7% had hearing loss [13]. In this study we found that none of the patients with OI had hearing loss. The binomial probability was calculated to be 0.2175 which does not disprove the prevalence rate Kuurila et al. found.

In the Impedance tympanometry tests, only two patients were found to have As curve in one ear each (Fig. 1). This could possibly be due to a resolving otitis media. However, both patients had intact DPOAES and the pure tone audiometry was well within the normal hearing thresholds for both patients. 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. found that none of the patients who received bisphosphonates had significant hearing loss [14]. 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 is 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, in fact 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 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 Zoledronic 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.

Research funding

No research grant was utilized for the study conducted.

Ethical approval

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the Helsinki guidelines.

Declaration of competing interest

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

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