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Observed Frequency and Characteristics of Hearing Loss in Osteogenesis Imperfecta

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ABSTRACT

***Background**: Osteogenesis imperfecta (OI) is a rare group of genetic disorders affecting connective tissue, with consequent bone fragility, frequent fractures and skeletal deformity. Depending on the type, patients can have blue sclera, dentinogenesis imperfecta, and hearing loss.* ***Aim**: To determine the frequency, type and audiometric characteristics of hearing loss in a group of patients with OI.* ***Material and Methods**: A prospective cohort study was completed. A clinical and diagnostic hearing evaluation with tympanometry, acoustic stapedial reflex, pure-tone and speech audiometry were performed.* ***Results:** Thirty patients completed the study; mean age of 22 years (range 6-63 years). Sixty seven percent had a type I OI. Overall, nine (30%) patients had hearing loss (15/60 ears). Of these, six had bilateral hearing loss. Of the 15 affected ears, six showed conductive hearing loss, five sensorineural hearing loss, and four mixed hearing loss. Patients with hearing loss were older than patients with normal hearing. Only one pediatric patient developed hearing loss. Of the ears without hearing loss, 13% did not have an acoustic stapedial reflex.* ***Conclusions:** In this group of patients with OI, 30% had hearing loss and among those ears with normal hearing, 13% did not have an acoustic stapedial reflex. Patients with OI should be monitored for hearing loss.*

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***Key words:** Hearing Loss; Osteogenesis Imperfecta; Otosclerosis; Reflex, Acoustic.*

Frecuencia y características de hipoacusia en osteogénesis imperfecta

***Antecedentes**: La osteogénesis imperfecta (OI) es un grupo raro de trastornos genéticos que afectan al tejido conectivo, con la consiguiente fragilidad ósea, fracturas frecuentes y deformidad esquelética. Según el tipo, los pacientes pueden presentar escleras azules, dentinogénesis imperfecta e hipoacusia.* ***Objetivos**: Determinar la frecuencia, tipo y características audiométricas de la hipoacusia en un grupo de pacientes con OI.* ***Material y Métodos**: Se completó un estudio de cohorte prospectivo. Se realizó una evaluación clínica, y de la audición con timpanometría, reflejo estapedial, audiometría tonal y logoaudiometría.* ***Resultados**: Treinta pacientes completaron el estudio; edad media de 22 años (rango 6-63 años). El 67% tenía una OI tipo I. Nueve pacientes (30%) tuvieron hipoacusia (15/60 oídos). De estos, seis tenían hipoacusia bilateral. De*

los 15 oídos afectados, seis tenían hipoacusia de conducción, cinco hipoacusia neurosensorial y cuatro hipoacusia mixta. Los pacientes con hipoacusia eran mayores que los pacientes con audición conservada. Sólo un paciente pediátrico desarrolló hipoacusia. De los oídos sin hipoacusia, el 13% tenía un reflejo estapedial ausente. ***Conclusiones:*** *En este grupo de pacientes con OI, el 30% tenía hipoacusia. Además, el 13% de los oídos con audición normal no tenía reflejo acústico estapedial. Los pacientes con OI deben ser monitoreados para detectar hipoacusia.*

Palabras clave: *Hipoacusia; Osteogenesis imperfecta; Otosclerosis; Reflejo acústico.*

Osteogenesis imperfecta (OI) is a genetically heterogeneous connective tissue disorder. It is a rare disease, with an estimated prevalence of 1:10,000 and to date, there is no cure. These patients have increased bone fragility and low bone mass with consequent frequent fractures and bone deformities. They may have scoliosis, short stature, ligamentous laxity, and also many extra-skeletal manifestations[1]. Because of its heterogenous clinical presentation, a classification of four different types of OI (I-IV) was initially created by Sillence *et al* in 1979. However, the classification has evolved substantially since then as genetic testing has allowed the identification of new subtypes, with a total of 19 genetic subtypes described up to now[1-3].

Most cases (85-90%) are due to mutations of the genes encoding type I collagen (COL1A1, COL1A2), which is the main component of the extracellular matrix found in bone and skin. All four initial types of OI involves either of these genes[1]. With advancements in sequencing, non-collagen genes have been identified to be involved in OI including genes encoding for proteins that are involved in collagen processing, bone cell differentiation, and mineralization[2,4].

It has been described that patients with OI can develop hearing loss (HL). It is believed that HL is a result of a variety of abnormalities, which seem to be different depending on the type of OI. Temporal bones of OI patients show delayed patterns of ossification, otosclerotic lesions, microfractures of the ossicles, stapes footplate fixation and/or obliteration of the round window[5-8]. As a result, patients can develop conductive (CHL), sensorineural (SNHL) or mixed HL[5].

Because it is a rare disease, and varies clinically based on the subtype, the prevalence of HL in OI patients has not been clearly described, varying between 2 and 94%[5]. Most case-series on this subject originate from North America, Europe and Australia[5,9,10]. To the best of our knowledge, there are only two articles reporting HL in OI patients from South America; a case series from Brazil, and a pediatric case-series from Venezuela[11,12].

The objective of this study was to determine the frequency of HL in patients suffering from OI in Chile. The main outcome was the presence of HL, and the secondary outcomes were to describe the types of HL and evaluate the presence of the stapedial reflex.

Materials y Methods

Ethics approval

Ethics approval for this study was obtained from the research ethics committee at the Pontificia Universidad Católica de Chile. All procedures performed were in accordance with the ethical standards of the institutional research committee, and with the Helsinki Declaration. Written informed consent was obtained from all patients involved in the study. For children, an informed permission of the parents with the assent of the child was recorded.

Patient selection

All patients with a diagnosis of OI under medical follow-up at the pediatric endocrinology department at the Pontificia Universidad Católica were contacted and invited to participate in this study. We identified 91 patients: 15 refused to participate, 43 could not reached, and 15 were interested but could not participate as they live in other regions of the country, and because of their disability, could not travel safely to Santiago. We, therefore, included 18 patients. Because of poor

accrual, we contacted the OI Foundation of Chile (FOICH: *Fundación de Osteogénesis Imperfecta Chile*), and invited their members to participate, an additional 12 participants we added with a final number of participants for the study totalling n = 30. Demographics, family history of OI, treatments for OI, and HL risk factors were recorded.

Audiological evaluation

Patients recruited in this study had a complete clinical otolaryngology examination. A tympanometry, acoustic stapedial reflex measurement, pure-tone audiometry and speech discrimination were then performed. Pure-tone air conduction thresholds and bone conduction thresholds were obtained for the frequencies 128, 256, 512, 1024, 2048, 3000, 4096, 6000 and 8196 Hz. Any frequency with a threshold of 20 dB or greater was considered as HL. HL at 1024 Hz or lower is considered low frequency HL, while HL at 2048 or greater is considered high frequency HL. The severity of HL was defined as mild when the average shift for the frequencies with a threshold of 20 dB or greater was 20-40 dB, moderate if 41-60 dB, and severe if over 61 dB. The Mann-Whitney U test was used to calculate differences between patients with and without HL.

Table 1. Patient demographics

Total	n = 30 (%)
Gender	
Male	20 (66.7%)
Female	10 (33.3%)
Age:	
Mean ± st dev.	22 ± 12.7 yrs
Median	20 yrs
Range	6-63 yrs
0 - 10 yrs	6 (20%)
11 - 20 yrs	9 (30%)
21 – 30 yrs	6 (20%)
31 – 40 yrs	6 (20%)
41 – 50 yrs	1 (3%)
51 – 60 yrs	0
61 yrs and over	1 (3%)
Pediatric patients (< 18 yrs)	12 (40 %)
OI type	
I	20 (66.7%)
II	0
III	6 (20%)
IV	4 (13.3%)
Family history	
Maternal line	7 (23%)
Paternal line	9 (30%)
Neonatal hearing screening	7 (23%) – all passed

Results

Demographics

Patient characteristics are described in Table 1. The median was 20 years, and 40% were less than 18 years old. Most of the patients evaluated were from the Santiago Metropolitan region (Figure 1). Only seven patients refer neonatal hearing

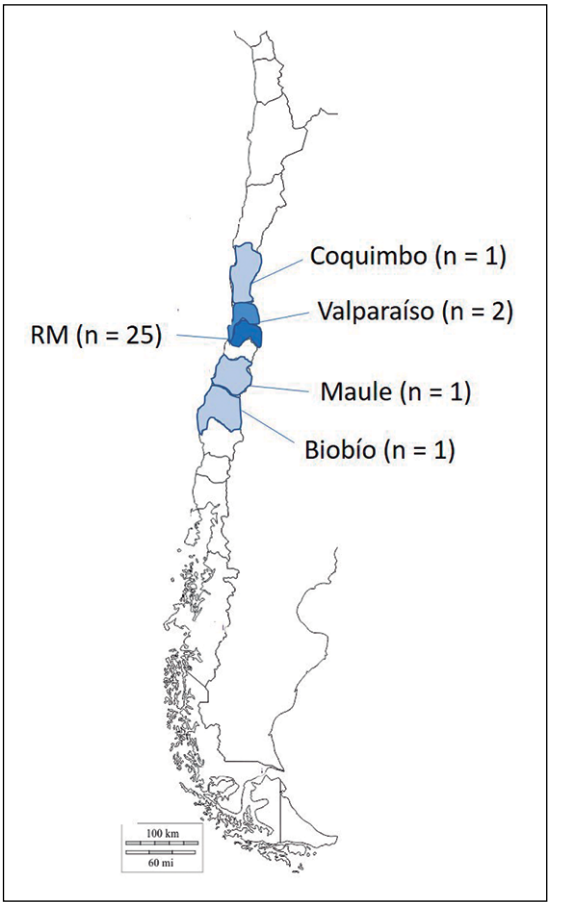

Figure 1. National distribution of the patients recruited in the study. Most of the patients were from the Santiago Metropolitan region. However, cases were also seen from neighbouring regions.

screening, and for all, results were normal. As for HL risk factors, no patients refer temporal bone fractures, noise exposure, or use of ototoxic medications; 4 refer neonatal hyperbilirubinemia (no treatment required), 5 were low birthweight (only 1 < 1500 g), 1 had a history of grommets for otitis media with effusion (resolved), and 1 had a history of an ear surgery (a unilateral atticotomy with normal hearing following surgery).

Tympanometry and acoustic stapedial reflex measurement

Normal tympanograms were observed for 88.3% of the ears (n = 53/60). Abnormalities were seen in: 3 ears with Ad curves, 2 ears with As curves, 1 ear with A double peak, and 1 ear with a C curve. The acoustic stapedial reflex was absent in 28.3% of ears (n = 17/60).

Pure-tone audiometry

Overall, 30% of patients had HL (n = 9/30; 15/60 ears). Of these 9 patients, 6 has bilateral HL. Of the 15 affected ears, 6 showed CHL, 5 showed SNHL, and 4 showed mixed HL. An example of unilateral CHL can be seen in Figure 2. HL severity was as follows: mild in 6 ears, moderate in 5 ears, and 4 ears were severe. Most presented HL through all of the frequencies (66.7% = 10/15 ears) while 2 ears were affected in the low frequencies only, and 3 were affected in the high frequencies only. Of the ears without HL, 13.3% did not have an acoustic reflex (n = 6/45). Also, HL was most common in type I OI (66.7%). In the adult group (n = 18/30), patients with HL were, on average, twelve years older than patients with normal hearing. HL was not more frequent in the female gender. When comparing adults with and without HL, statistically significant hearing threshold shifts were seen for all of the tested frequencies (Table 2). In the pediatric group, only one patient presented a mild SNHL in the high frequencies (n = 1/12).

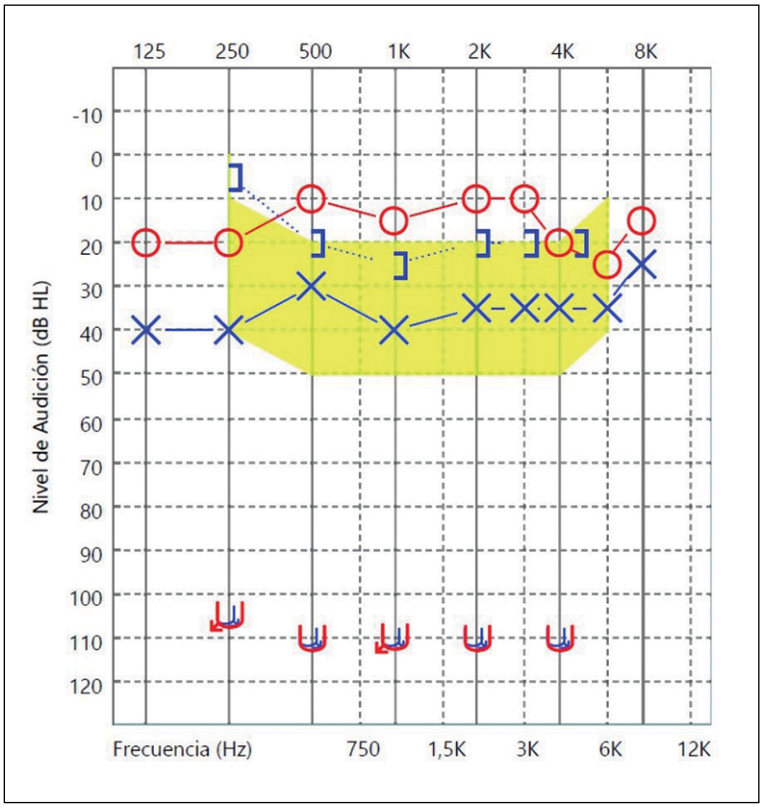

Figure 2. Example of hearing loss on a pure-tone audiogram. This audiogram shows a conductive hearing loss for the left ear for a 28-yeard old female patient. Red circles depict normal hearing thresholds for the right ear, while the blue "X" (air conduction) and "]" (bone conduction) depict a conductive hearing loss for the left ear. An air-bone gap can be seen for the left ear for the frequencies of 250 Hz to 4 kHz.

Table 2. Audiological findings for adults (≥ 18 years) with osteogenesis imperfecta

	Without hearing loss	With hearing loss	Mann-Whitney U test (p-value)
Age[a]	24.2 ± 6.2 yrs	36.2 ± 11.9 yrs	0.0014*
Gender (female)	n = 7 / 10	n = 5 / 8	0.8258
Average hearing threshold[a] (dB)			
128 Hz	13.8 ± 4.6	42.8 ± 21.4	< 0.0001*
256 Hz	13.0 ± 4.1	46.0 ± 25.9	< 0.0001*
512 Hz	10.3 ± 5.3	41.3 ± 28.3	0.0004*
1024 Hz	12.3 ± 5.3	43.1 ± 30.4	0.0003*
2048 Hz	9.0 ± 7.5	37.5 ± 31.8	0.0003*
3000 Hz	6.75 ± 7.8	34.4 ± 28.6	0.0003*
4096 Hz	8.3 ± 7.3	39.4 ± 29.9	0.0003*
6000 Hz	10.3 ± 6.2	47.2 ± 29.9	0.0003*
8196 Hz	9.5 ±6.9	44.6 ± 31.8	0.0001*
Pure-tone average[b]	10.2 ± 5.3	36.5 ± 25.6	0.0010*
Speech discrimination (%)	100 ± 0.0	89.3 ± 27.2	0.3472

[a]Mean ± standard deviation. [b]Pure-tone average was calculated as the average of hearing sensitivity at 512, 1024, 2048 and 4096 Hz. *Statistically significant p-values (p ≤ 0.05). Yrs: years, dB: decibel.

Discussion

While OI is a rare disease, patients suffering from OI will be seen by various medical specialists, it is therefore important for clinicians to know the clinical phenotypes. It has been described that patients with OI can develop HL. However, no prior studies have evaluated the presence of HL in Chilean patients. We found an overall frequency of HL of 30%. It is believed that HL begins in early adulthood and progresses with time. Kuurila *et al* describe a mean age of onset of 29 years, and our cohort had a mean age of 22 years[13]. Therefore, it is expected that more patients will develop HL after this study is completed. It is also believed that there may be some similarities with otosclerosis, known to be more frequent in female patients[14,15]. We did not observe a difference for gender. We speculate that HL in OI is unrelated to gender[5,13].

Children with OI can also develop HL, but it is uncommon, and when present, tends to be conductive. We describe only on pediatric patient with SNHL. Of importance in this group is the potential of treatment to decrease the incidence or severity of HL. It has been suggested that bisphosphonates, by inhibiting bone resorption, could delay the progression of HL by improving middle and inner ear ossification[5]. All patients with OI should be monitored for HL, and should include tympanometry with acoustic stapedial reflex, and pure-tone audiometry[15-17]. It has been suggested to begin monitoring around the age of 10 years, and follow-up every three years, depending on the case[13]. It is important to remember that patients can have a normal audiogram but an absent acoustic stapedial reflex, this could be an early sign of CHL[14]. The stapedial reflex consists in the middle ear muscles stiffening the ossicular chain when presented with a high-intensity sound stimulus. It has been shown that for diseases with stapes footplate fixation, such as OI, the reflex may be absent before hearing loss is observed[16,18]. Once HL is detected treatment includes hearing aids and, is some cases, surgery (stapedotomy)[2,5]. A multidisciplinary approach is ideal for the management of these patients.

This study has some limitations. Because of the small sample size, we could not determine the prevalence of HL in OI. Hence, we describe our results as observed frequencies. Also, since HL in OI increases with age and many of our patients evaluated were around or younger that 18 years-

old, our results could have underestimated the observed frequency of HL.

Conclusion

Patients with OI can develop conductive, sensorineural or mixed hearing loss which progresses with time. It is rarely seen in pediatric patients; however, monitoring for hearing loss should began at this stage. All patients with OI should be monitored for hearing loss. While patients may not develop hearing loss initially, the acoustic stapedial reflex can be absent as an early sign of a future conductive hearing loss.

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