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Abstract

Objectives: The objective of this prospective study was a longitudinal analysis of the progression of hearing thresholds in patients with osteogenesis imperfecta (OI).

Methods: Audiometric results from thirty-six OI patients (6-79 y) were compared between two test moments with an average interval of four years. Audiometric evaluation included acoustic admittance measurements, acoustic stapedial reflex measurements, pure-tone audiometry and otoacoustic emissions.

Results: Air conduction pure tone average (PTA), corrected for sex and age, and bone conduction PTA increased significantly in the study population ($P<0.05$ and $P<0.001$, respectively). In 14.3% of the evaluated ears, an alteration in type and/or severity of hearing loss was observed.

Conclusion: After an average time interval of 4 years, significant changes in hearing status occur in a population of OI patients. These findings highlight the importance of regular audiologic follow-up in patients with OI, including audiometry, acoustic admittance measurements, acoustic stapedial reflexes and otoacoustic emissions.

Key words: Osteogenesis imperfecta; hearing loss; longitudinal study.

Longitudinal analysis of audiologic phenotype in osteogenesis imperfecta: a follow-up study

Summary

- Hearing loss affects about half of the subjects with osteogenesis imperfecta (OI)
- Hearing loss in OI usually appears as a conductive hearing loss in the second to fourth decade of life and evolves to a mixed hearing loss.
- Sensorineural hearing loss occurs in a minor proportion of the OI patients, is less progressive and may arise at any age.
- This follow-up study in OI patients demonstrates a significant progression of hearing thresholds within an average time interval of four years that exceeds the normal age- and sex-related physiological hearing deterioration.

1. Introduction

Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder with a prevalence of approximately 1/15.000 - 1/20.000 individuals without gender or ethnic preponderance.[1] The hallmark features of this clinically heterogeneous syndrome are bone fragility, growth deficiency and bone deformity. Other common characteristics are blue sclerae, hearing loss, dental abnormalities and joint hyperlaxity.[2]

The classical Sillence OI types (I – IV)[3] with autosomal dominant (AD) inheritance account for 85-90% of the cases[4]. In type I, the most frequent type, the patients have blue sclerae, hearing problems and multiple fractures due to osseous fragility. Type II refers to perinatally lethal OI, in which inferior skull ossification, long bone deformities, fractures of the ribs and pulmonary insufficiency are observed. Patients with the severe, non-lethal OI type III suffer from progressive deformation of the skeleton, abnormal dentine, blue sclerae, short stature and scoliosis. Type IV, known as the moderate AD form, is characterised by a variable short stature, long bone deformities and, sometimes, blue sclerae.[3] These four AD OI types are caused by a wide variety of mutations in the genes *COL1A1* and *COL1A2*. Mutations affecting these genes induce abnormalities in the quantity or structure of type I collagen, which is an important protein in bone, skin, sclerae, ligaments and tendons.[4]

In the last decade, mutations in other genes that contribute to the posttranslational modification, folding and cross-linking, mineralisation, and osteoblast differentiation of type I collagen have been related to the more uncommon, autosomal recessive forms of OI. Consequently, the classification as mentioned above has recently been extended with OI types V to XVI and even more types are expected to be recognised in the future.[2]

Hearing loss is diagnosed in about half of the patients with AD OI types I, III and IV.[3,5-7] The hearing loss is heterogeneous in terms of onset, type, severity and progression. In addition, no

correlation is found between the presence, the configuration, the type or the severity of hearing loss and the other clinical OI characteristics, the type of OI or the mutation.[6-8] Typically, the hearing impairment associated with OI begins as a conductive type between the second to fourth decade of life and evolves to a mixed hearing loss due to progressive inner ear involvement.[6,9-14] Occasionally, it already manifests in childhood.[15] The conductive impairment is caused by ossicular dysfunction associated with otospongiotic changes of the temporal bone structures inducing stapes footplate fixation, and sometimes with microfractures or atrophy of the stapedial crura.[5,11,13,16] A concomitant sensorineural component arises when the otospongiotic changes proliferate to the retrofenestral labyrinthine bone.[17] Pure sensorineural hearing loss is observed in a minor proportion of OI adults and is generally less severe and less progressive in comparison with conductive or mixed hearing loss in OI.[14] Fractures of the cranium, inner ear hair cell loss, perilymph haemorrhage, abnormalities of the tectorial membrane and stria vascularis have been suggested to be the underlying pathologies of a sensorineural hearing loss in OI.[10,13]

Since a gradually increasing hearing loss manifests in both OI adults and children, audiological screening and monitoring in patients with OI is recommended. Timely intervention with hearing aids or appropriate middle ear surgery may prevent hearing impaired OI children from psychosocial, learning and developmental difficulties. Secondly, consecutive audiological testing is also beneficial in adults because they often underestimate the degree of hearing loss.[6] There is limited knowledge about the progression of the OI related hearing loss. On the basis of a cross-sectional study in OI type I patients, Garretsen et al. (1997) concluded that the gradual increase of OI related hearing loss with age was significantly higher than the increase in hearing loss due to presbyacusis.[18] Age-related threshold audiograms (ARTAs) for both, conductive/mixed and sensorineural hearing loss have been developed in another cross-sectional study.[14] However, longitudinal research

investigating the progression of hearing loss in OI is lacking. In contrast with cross-sectional surveys, longitudinal research avoids cohort effects and may describe the progression of hearing loss in both individual OI patients and a group of OI patients. The purpose of the current follow-up study is to longitudinally analyse the progression of OI related hearing loss.

2. Materials and methods

2.1. Subjects

Eighty-four Belgian OI patients who participated in a large study investigating the audiologic phenotype of OI were invited to participate in a follow-up study[14]. Forty-two patients (84 ears) agreed to participate. The study was approved by the Ethics Committee of the Ghent University Hospital (UZ Ghent). In accordance with the Declaration of Helsinki, informed consent was obtained in all subjects before participation.

Ears with a history of stapes surgery or with a suspicion of hearing loss due to other causes than OI were precluded from the analysis in order to reliably map the progression of the OI related hearing loss. Six patients were excluded from the analysis because they were bilaterally operated for stapes surgery. From two patients with unilateral stapes surgery only the results of the non-operated ear were included in the analysis. There was no clinically relevant noise exposure in this group of patients.

The audiometric follow-up evaluation comprised acoustic admittance and acoustic stapedial reflex (ASR) measurements, pure-tone audiometry, transient evoked and distortion product otoacoustic emissions (TEOAEs and DPOAEs). The same protocol was applied to both adult and paediatric OI patients.

a. Audiologic follow-up evaluation

2.2.1. Acoustic admittance and ASR measurements

Tympanograms were acquired bilaterally by means of an 85-dB SPL 226-Hz probe tone (TympStar, Grason Stadler Inc., MN, USA). The pressure in the ear canal fluctuated from -400 to +200 daPa. The tympanograms were classified into the following types: A, Ad, As, B and C, as defined by Jerger (1970)[19].

Ipsilateral ASR thresholds were obtained bilaterally for a stimulus at 1.0 kHz (TympStar, Grason Stadler Inc., MN, USA). The acoustic reflex threshold (ART) was defined as normal within the range of 70 and 100 dB SPL, with an admittance deflection of more than 0.02 ml.[20]

2.2.2. Pure-tone audiometry

Auditory sensitivity was assessed bilaterally applying the Hughson-Westlake method in a sound-isolated room with double walls and using the Equinox 2.0. PC-based audiometer (software OtoAccess 1.2.1, Interacoustics, Assens, Denmark). Air conduction (AC) thresholds (dB HL) were measured at eight audiometric frequencies (0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz) with a TDH-39 headphone. Bone conduction (BC) thresholds (dB HL) were determined at five octave-frequencies (0.25, 0.5, 1.0, 2.0 and 4.0 kHz). Contralateral narrow band masking noise was used to obtain masked AC thresholds when the inter-aural differences in AC or the differences between the AC thresholds and the contralateral BC thresholds were larger than 40 dB. An air-bone gap (ABG) beyond 10 dB required contralateral masking noise to determine masked BC thresholds.

The pure tone-average (PTA) was computed for AC and BC of each ear by averaging the thresholds at 0.5, 1.0 and 2.0 kHz. The high-frequency (HF) PTA was calculated by averaging the AC thresholds at 4.0, 6.0 and 8.0 kHz. In addition, the average ABG at 0.5, 1.0 and 2.0 kHz was computed. Hearing was classified as (I) normal hearing: PTA AC < 15 dB HL and average ABG < 15 dB; (II) conductive hearing loss: PTA BC < 15 dB HL and average ABG ≥ 15 dB; (III) pure sensorineural hearing loss: PTA AC ≥ 15 dB HL and average ABG < 15 dB; (IV) high-frequency sensorineural hearing loss: HF PTA > 30 dB HL; (V) mixed hearing loss: PTA BC ≥ 15 dB HL and average ABG ≥ 15 dB or (VI) undefined hearing loss: BC thresholds are undefined due to a limited audiometer output.[14] By comparing the pure-tone thresholds with the 95th percentile value for sex- and age-related hearing thresholds (ISO-7029)[21], OI related hearing loss could be distinguished from presbyacusis. If application of the

abovementioned criteria pointed towards a conductive, sensorineural, high-frequency sensorineural or mixed hearing loss and the AC thresholds at three or more frequencies exceeded the ISO-7029 values, the presence of OI related hearing loss was confirmed. The diagnosis of hearing loss was disapproved when the AC thresholds corresponded with the 95th percentile normal threshold values.

The severity of the hearing loss was classified as (1) mild when the air conduction PTA was at least 15 dB HL and better than 40 dB HL; (2) moderate when the air conduction PTA was at least 40 dB HL and better than 70 dB HL; (3) severe when the air conduction PTA was at least 70 dB HL and better than 95 dB HL; or (4) profound when the air conduction PTA was at least 95 dB HL.[14]

2.2.3. Otoacoustic emissions

TEOAE and DPOAE were both examined in a sound-isolated room with double walls. The signal-to-noise ratio (SNR) was used to determine the presence of TEOAEs and DPOAEs at each frequency from 1.0 to 4.0 kHz and 1.0 to 8.0 kHz, respectively.

TEOAE measurements were performed by using an acoustic click with a duration of 80 µsec, an intensity of 80 dBpeSPL and alternating polarity (Otoport Advanced ILOV6 software, Otodynamics, Hertfordshire, United Kingdom). In general, TEOAEs were considered as present if at least three out of five frequency bands showed SNR of at least 3 dB.[22]

In DPOAE measurements, two pure tones were delivered with a frequency ratio of 1.22 (f_2 / f_1 = 1.22; $f_2 > f_1$) and an intensity (I) of 65 and 55 dB SPL ($I_1 > I_2$), resulting in the measurement of the combination tone ($2f_1$-f_2) (Otoport Advanced ILOV6 software, Otodynamics, Hertfordshire, United Kingdom). DPOAEs were considered as present if at least five out of seven frequency bands showed SNR of at least 3 dB.[23, 24]

2.3. Statistical analysis

Data were analysed with SPSS version 21.0. Descriptive statistics were performed to compare the prevalence of normal or aberrant results from the first and second evaluation for each audiologic test. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were applied to evaluate the normal distribution of continuous variables. The Wilcoxon matched-pairs signed-ranks test was used to compare thresholds averaged over three frequencies between both audiometric evaluations, because normal distribution was not achieved in these variables. In all analyses, a significance level of 0.05 was applied.

3. Results and analysis

3.1. Characteristics of the population

Measurements corresponding to 70 ears from 36 different subjects aged 6-79 years (including both ears of 34 patients and one ear of two patients with unilateral stapes surgery) at first audiologic evaluation (FE) and second audiologic evaluation (SE) were analysed to map the progression of OI related hearing loss. The population characteristics are summarised in Table I. Mean time interval between FE and SE was four years and one month (SD = 8 months).

3.2. Audiometric evaluation

The AC PTA, BC PTA, HF PTA and the average ABG of all 70 ears were compared between both evaluations. A significant increase of AC PTA ($P<0.001$, Wilcoxon signed-ranks test), BC PTA ($P<0.001$, Wilcoxon signed-ranks test) and HF PTA ($P<0.001$, Wilcoxon signed-ranks test) was found at SE, in comparison with FE. In contrast, the average ABG did not significantly differ between both evaluations (Wilcoxon signed-ranks test). In order to preclude that the significant increases of AC PTA and HF PTA at SE were caused by an increase of age at SE, AC PTAs and HF PTAs at both FE and SE were subtracted from the averaged 95^{th} percentile values for sex- and age-related hearing thresholds (ISO-7029). The difference between AC PTA and sex- and age-related thresholds was significantly larger at FE compared to SE ($P<0.05$, Wilcoxon signed-rank test). In contrast, no significant differences were found between the age- and sex-corrected HF PTAs at FE versus SE (Wilcoxon signed-ranks test).

Hearing was impaired in 22/60 adult ears (36.7%) at FE, and in 24/60 adult ears (40.0%) at SE. No hearing loss was identified in the 10 evaluated children. The different types of hearing loss are shown in Figure 1. Occurrence and type of hearing loss were not associated with the clinically diagnosed OI type (Table II). The severity of hearing loss is represented in Figure 2. The severity and type of hearing loss were compared between FE and SE. Ten hearing-impaired ears showed an alteration in severity and/or type of hearing loss from FE to SE, all of which are listed in Table III.

3.3. Acoustic admittance measurements

Acoustic admittance measurements were performed in 69/70 ears (98.6%) at FE and in 65/70 ears (92.9%) at SE. Measurements were missing in one ear with a moderate mixed hearing loss at FE and SE because stapes surgery was performed in the other ear before FE and patient was fearing the test. Furthermore, acoustic admittance measurements were not performed in both ears of a 79-year-old subject with severe and profound undefined hearing loss at SE to limit the test time for this subject. In another subject fearing this test with bilateral high-frequency sensorineural hearing loss, acoustic admittance measurements were not available at SE.

Tympanograms type A were most prevalent: 75.4% (52/69) of the ears at FE and 73.8% (48/65) of the ears at SE. Type Ad tympanograms were found in 18.8% (13/69) of the ears at FE and in 18.5% (12/65 ears) of the ears at SE. No association is found between the type of tympanogram and the occurrence or type of hearing loss. In the remaining ears, tympanograms type As (1.4% or 1/69 ears at FE and 7.7% or 5/65 ears at SE), type B (2.9% or 2/69 ears at FE) and type C (1.4% or 1/69 at FE) were obtained.

Acoustic admittance measurements were performed in 65 ears at both evaluations. In 11 of these ears (16.9%), the type of the tympanogram was different at FE compared to SE. All ears with an altered tympanometric shape had an unaltered type of hearing loss. Two of these ears (Case No: 20 R, 20 L, Table III) showed a change in severity of the hearing loss.

3.4. Ipsilateral ASR measurements

ASRs were measured in 67/70 ears (95.7%) at FE and in 65/69 ears (92.9%) at SE. However, no measurements were obtained for the ears already described in section 3.3. In addition, ASR measurements were missing in two more ears (Case No: 5 R, 5 L) corresponding to a six-year-old boy at FE.

In the majority of the ears with normal hearing ASRs were elicited at both measurements: in 91.3% and 84.8% of the ears with normal hearing at FE and SE, respectively. At both evaluations, ASRs were absent in all ears with a conductive hearing loss component and in most of the ears with sensorineural or high-frequency sensorineural hearing loss.

In 63 ears ASRs were performed at both evaluations. In ten ears, a change in the presence of ASRs between both measurements took place. In four normal-hearing ears and one ear with a mild high-frequency sensorineural hearing loss, ASRs were registered at FE but were absent at SE without an alteration in the presence or type of hearing loss. However, HF PTA increased in one of these normal-hearing ears from 6.7 dB HL at FE to 18.3 dB HL at SE and in another ear from 8.3 dB HL to 16.7 dB HL. In one ear with a mild mixed hearing loss at both measurements, ASRs were absent at FE, but present with an ART of 100 dB SPL at SE. The average ABG in this ear changed from 30 dB at FE to 15 dB at SE. One normal-hearing child had bilateral absent ASRs at FE, but present ASRs at SE. The average ABG in this subject decreased from 6.7 dB (right ear) and 11.7 dB (left ear) at FE to 0.0 dB in both ears at SE, and the tympanogram changed from type B to type As bilaterally. The hearing changed in one ear (Case No: 16 L, Table III) from normal-hearing with a present ASR to high-frequency sensorineural hearing loss with an absent ASR. In another subject, both ears (Case No: 28 (right and left ear), Table III) changed from normal-hearing with a present ASR to mild sensorineural hearing loss with an absent ASR.

3.5. Otoacoustic emissions

TEOAEs and DPOAEs were only measured at SE, in 68 out of 70 ears.

3.5.1. TEOAEs

TEOAEs were absent in 22 out of 68 ears (32.4%), i.e. in three normal-hearing ears, two ears with mild conductive hearing loss, two ears with mild sensorineural hearing loss, ten ears with mixed hearing loss, two ears with profound hearing loss and three ears with high-frequency sensorineural hearing loss, of which two had a mild severity and one a moderate severity.

Conversely, TEOAEs with an SNR of at least 3 dB at three or more frequency bands were found in 43 normal-hearing ears and three ears with sensorineural hearing loss. In these 43 normal-hearing ears, TEOAEs at 1.0 and 4.0 kHz were more often absent in comparison with TEOAEs at 1.4, 2.0 and 2.8 kHz (Table IV). TEOAEs at 2.0, 2.8 and 4.0 kHz were present in all three ears with mild sensorineural hearing loss. In one of these ears, TEOAEs were present at all frequencies. In the lower frequencies (1.0 and 1.4 Hz), TEOAEs were absent in two ears with sensorineural hearing loss (Table IV).

3.5.2. DPOAEs

In 18 out of 46 normal-hearing ears (39.1%), DPOAEs were present at all seven frequencies. In 16 normal-hearing ears (34.8%), DPOAEs were present at six frequencies. Nevertheless, DPOAEs were present at less than five frequencies in 6 (13%) normal-hearing ears. DPOAEs at 8.0 kHz were present in less than 50% of the normal-hearing ears, whereas DPOAEs at all other frequencies (1.0, 1.4, 2.0, 2.8, 4.0 and 6.0 kHz) were present in about 80 to 90% of these ears (Table V).

4. Discussion

Hearing loss has been reported to affect about half of the osteogenesis imperfecta patients.[5-6,9,11,14] The present study is the first attempt to longitudinally map the progression of OI related hearing loss. The audiologic results of a comprehensive audiometric evaluation in 36 osteogenesis imperfecta patients were compared with those of a second audiometric evaluation with an average test time interval of four years.

Overall statistically significant increases in average AC PTA and BC PTA were found at SE compared to FE. This progression of hearing thresholds could not be explained by physiological age-related hearing deterioration since a significantly higher difference between AC PTA and the 95th percentile of sex- and age-related thresholds (ISO-7029)[21] was found at SE in comparison with FE. However, no significant difference was found between the average ABG at FE versus SE. Therefore, the increase of hearing thresholds in OI is predominantly determined by progression of the sensorineural component, which has already been suggested by cross-sectional research in OI[14,18].

Pure-tone audiometry demonstrated that hearing was impaired in 31.4% (i.e. 22/70) and 34.3% (i.e. 24/70) of the ears at FE and SE, respectively. The increasing prevalence of hearing loss after a four-years interval, as demonstrated in the present study, is in line with the reported increase in prevalence of hearing loss with advancing age in other studies.[10,11,13,14]

The OI related hearing loss typically starts with a conductive loss before the age of forty years, most often due to stapes footplate fixation, and evolves to mixed hearing loss over time.[6,9-14] However, at SE we noticed the onset of a mild sensorineural hearing loss in three ears, corresponding to two subjects aged younger than 40 years. In another ear, mild sensorineural hearing loss at FE changed into a conductive hearing loss at SE. Due to the criteria used to define hearing loss, early conductive loss with a small ABG might have been classified as mild sensorineural hearing loss. Measurement of ASRs and OAEs in addition to pure-tone audiometry is recommended in the OI population in order to make a differential diagnosis between early conductive and sensorineural

hearing loss. Absent ASRs and absent OAEs in ears classified as mild sensorineural loss on the basis of the audiogram suggest a conductive component, since ASRs and OAEs are usually still elicitable in sensorineural losses with audiometric thresholds better than 50-60 dB HL. Other changes in the type of hearing loss in the present study also demonstrate variability in audiometric threshold measurement accuracy, since in one ear sensorineural hearing loss across all frequencies evolved to sensorineural hearing loss at high frequencies only and, in another ear, a mild sensorineural hearing loss disappeared. The importance of a test battery comprising audiometry, admittance measurements and OAE registration is emphasised in order to detect early changes in hearing sensitivity and to more accurately determine the site of lesion.

Similar with other studies reporting on hearing loss in OI, the hearing loss severity ranged from mild to profound. Between FE and SE little difference was observed in the numbers of ears corresponding to the different categories of hearing loss severity, which may be attributed to the relatively short test time interval. In addition, this longitudinal study could not offer a reliable estimation of the average annual threshold deterioration in hearing-impaired OI patients since the obtained thresholds deviated from the normal distribution and because of the small amounts of patients in some categories of hearing loss types. A cross-sectional study in hearing-impaired OI patients with conductive or mixed hearing loss revealed annual increases of 0.6 dB/year and 0.4 dB/year for AC PTA and BC PTA, respectively.[14] Similar with the present study, the average ABG remained relatively stable over time.[14] In OI patients with sensorineural hearing loss annual threshold deteriorations of 0.2 dB/year for AC PTA to 1.2 dB/year at 8.0 kHz were demonstrated.[14]

Abnormal acoustic admittance results were obtained in 24.6% and 26.2% of the evaluated ears at FE and SE, respectively. However, normal type A tympanograms were observed in OI ears corresponding to normal hearing as well as to different types of hearing loss. It was already noted in other studies[11,13,14] that tympanometric shape is not a good indicator for the different types of OI related hearing loss, due to the often thin, hypermobile tympanic membranes inherent to the affected type I collagen that characterises OI. Due to the connective tissue abnormalities affecting

both the ear drum and middle ear components, the interpretation of admittance results in OI patients may be complicated. Therefore, the registration of OAEs in addition to admittance measurements might be very helpful in the diagnosis of early conductive loss caused by stapes footplate fixation, which is the major problem in OI-related hearing loss. Otoacoustic emissions were recorded at SE to determine the functioning of the outer hair cells in subjects with OI. TEOAEs were absent in 32.4% of the ears. In general, TEOAEs were present in 93.5% of normal-hearing ears and in 50.0% of ears with mild sensorineural hearing loss. These results were within the expectations, since TEOAEs are absent in endocochlear sensorineural hearing loss higher than 30 dB HL and in ears with a conductive hearing loss component. In contrast, Pillion and Shapiro (2008)[13] concluded a moderate correspondence between the presence of abnormal TEOAEs and the presence of hearing loss in OI since they found absent TEOAEs in 13% of the normal-hearing ears, in 71% of the ears with conductive hearing loss, in 73% of the ears with mixed hearing loss and in 40% of the ears with sensorineural hearing loss. Nevertheless, their criteria used to define absent TEOAEs were different compared to our study: SNR was not taken into account but TEOAEs were judged as absent when reproducibility at two or more frequency bands was less than 70%[13]. In addition, TEOAEs are supposed to be absent in ears with a conductive component, which was confirmed by our results.

This is the first study reporting on the results of DPOAEs in OI patients. DPOAEs are expected to be absent in endocochlear sensorineural hearing loss above 55 dB HL and in hearing loss with a conductive component. In the present study, DPOAEs were absent in two ears with severe and profound undefined hearing loss and in all ears with conductive or mixed hearing loss. Additionally, DPOAEs were also considered as absent in four out of five ears with mild sensorineural hearing loss and in all ears with mild or moderate high-frequency sensorineural hearing loss. As mentioned before, early conductive hearing loss might, at least in some ears, have been classified as mild (high-frequency) sensorineural hearing loss, particularly in the ears with mild sensorineural loss on the basis of the audiogram in combination with absent DPOAEs and ASRs. In two ears with

sensorineural loss TEOAEs were present while DPOAEs were absent, which might be explained by a higher sensitivity of DPOAEs to the higher frequencies compared to TEOAEs. Given that OAE measurements may be used as an additional test to detect early conductive hearing loss, as well as outer hair cell dysfunction, it is recommended to include them in an audiologic follow-up protocol for patients with OI.

In summary, this study is the first attempt to a prospective, longitudinal follow-up of OI related hearing loss. Presence, type and/or severity of hearing loss changed in 14.3% of the ears after an average time interval of four years, and significant changes in median hearing thresholds were found between both evaluations. Although the relatively low percentage of altered hearing in this study, which is partially due to the limited number of subjects, we would like to encourage audiologic follow-up every three to four years in the OI population. This follow-up should comprise pure-tone audiometry, tympanometry, ASR and OAE measurements. A combination of these tests may help the clinician to detect early changes in hearing sensitivity or compliance of the middle ear. In addition, further follow-up is needed in order to map the audiologic progression in OI with more accuracy.

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TABLES

TABLE I
POPULATION CHARACTERISTICS

Characteristic	Adults*	Children (<18 years)†
Gender distribution (*n*)		
– Males	12	5
– Females	19	0
Age (mean ± SD; years)		
– At 1st evaluation	38.2 ± 14.0	8.6 ± 3.9
– At 2nd evaluation	42.3 ± 13.9	11.4 ± 4.6
Clinical osteogenesis imperfecta type (*n*)		
– Type I	24	4
– Type III	3	1
– Type IV	4	0
Mutated gene (*n*)		
– *COL1A1*	25	3
– *COL1A2*	6	2
Familial or isolated osteogenesis imperfecta (*n*)		
– Familial	24	2
– Isolated	7	3

*Total *n* = 31 (86.1%); †total *n* = 5 (13.9%). SD = standard deviation

TABLE II
HEARING LOSS OCCURRENCE AND TYPE AS A FUNCTION OF CLINICAL OSTEOGENESIS IMPERFECTA TYPE*

Hearing type	Osteogenesis imperfecta type (numbers of ears)		
	Type I	Type III	Type IV
Normal hearing	36	4	6
Conductive hearing loss	1	1	–
SNHL	8	–	2
High-frequency SNHL	3	2	–
Mixed hearing loss	5	–	–
Undefined hearing loss	2	–	–

*Total ears *n* = 70. SNHL = sensorineural hearing loss

TABLE III
OVERVIEW OF HEARING-IMPAIRED EARS WITH CHANGES IN HEARING LOSS SEVERITY AND/OR TYPE BETWEEN FIRST AND SECOND AUDIOMETRIC EVALUATION

Pt no.	Ear	Gender	Age at follow up (years)	Interval between evaluations	Audiometric result*					
					1st evaluation		2nd evaluation			
					Pure tone audiometry	ASR	Pure tone audiometry	ASR	TEOAE	DPOAE
14	L	F	56	3 y, 6 mth	Moderate SNHL	−	Moderate high-frequency SNHL	−	−	−
16	L	F	30	4 y, 4 mth	Normal	+	Mild high-frequency SNHL	−	−	−
20	R	F	54	4 y, 10 mth	Mild mixed hearing loss	−	Moderate mixed hearing loss	−	−	−
20	L	F	54	4 y, 10 mth	Mild mixed hearing loss	−	Moderate mixed hearing loss	−	−	−
22	L	F	41	5 y, 0 mth	Mild SNHL	−	Mild conductive hearing loss	−	−	−
25	L	F	32	3 y, 7 mth	Mild conductive hearing loss	−	Mild SNHL	−	−	−
28	R	F	35	3 y, 6 mth	Normal	+	Mild SNHL	−	+	+
28	L	F	35	3 y, 6 mth	Normal	+	Mild SNHL	−	+	+
29	L	F	45	3 y, 5 mth	Mild SNHL	−	Normal	−	−	−
35	L	F	69	4 y, 5 mth	Severe mixed hearing loss	−	Profound hearing loss	−	N/A	N/A

*Note that '+' indicates present and '−' represents absent. Pt no. = patient number; ASR = acoustic stapedius reflex; TEOAE = transient evoked otoacoustic emissions; DPOAE = distortion product otoacoustic emissions; L = left ear; F = female; y = years; mth = months; SNHL = sensorineural hearing loss; R = right ear; N/A = not available

TABLE IV
EARS WITH PRESENT TEOAES AT EACH FREQUENCY BAND*

Hearing type	Ears (*n*)	Frequency				
		1.0 kHz	1.4 kHz	2.0 kHz	2.8 kHz	4.0 kHz
Normal hearing	43	76.7	97.7	100	97.7	88.4
SNHL	3	33.3	33.3	100	100	100

Data represent percentages of ears, unless indicated otherwise. *Signal-to-noise ratio of more than 3 dB. TEOAEs = transient evoked otoacoustic emissions; SNHL = sensorineural hearing loss

TABLE V
EARS WITH PRESENT DPOAES AT EACH FREQUENCY BAND*

Hearing type	Ears (*n*)	Frequency						
		1.0 kHz	1.4 kHz	2.0 kHz	2.8 kHz	4.0 kHz	6.0 kHz	8.0 kHz
Normal hearing	46	82.6	80.4	91.3	89.1	89.1	89.1	45.7
Conductive hearing loss	2	50	–	–	–	–	–	–
SNHL	5	20	20	20	40	80	60	20
Mixed hearing loss	10	–	10.0	–	–	–	–	10.0
High-frequency SNHL	3	–	33.3	–	–	–	–	–
Profound hearing loss	2	–	–	–	–	–	–	–

Data represent percentages of ears, unless indicated otherwise. *Signal-to-noise ratio of more than 3 dB. Absence of any distortion product otoacoustic emission (DPOAE) response at a certain frequency band is indicated by '–'. SNHL = sensorineural hearing loss

Figures

Figure 1. Occurrence and types of hearing loss in 70 ears with osteogenesis imperfecta at first and second audiometric evaluation with a mean time interval of four years and one month.

SN=sensorineural, HF=high-frequency.

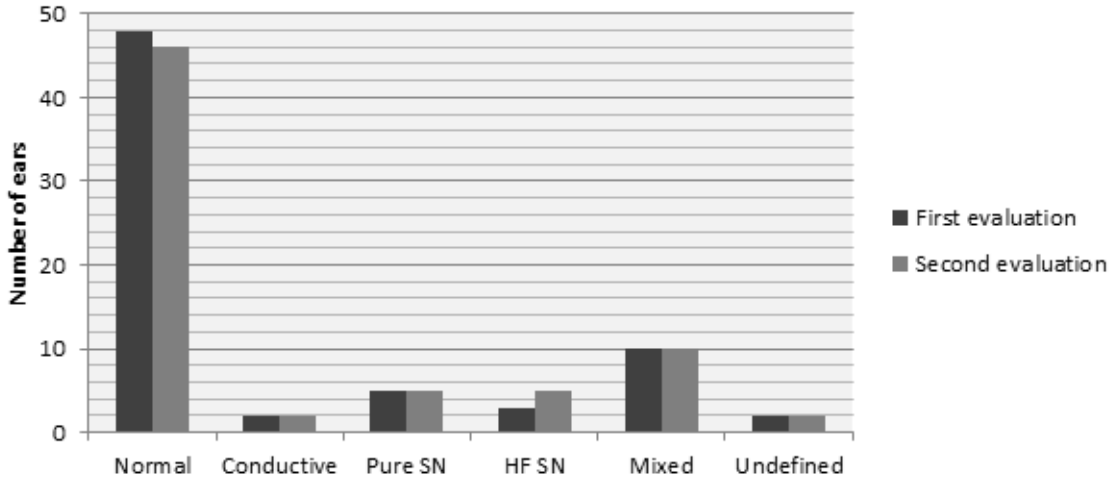

Figure 2. Severity of hearing loss in the hearing-impaired ears of osteogenesis imperfecta patients at first (n=22) and second (n=24) audiometric evaluation with a mean time interval of four years and one month.

Classification of severity is based on pure tone averages (PTA) of air conduction (AC) thresholds at frequencies 0.5, 1.0 and 2.0 kHz. Mild: 15 dB HL ≤ PTA AC < 40 dB HL; moderate: 40 dB HL ≤ PTA AC < 70 dB HL; severe: 70 dB HL ≤ PTA AC < 95 dB HL; profound: 95 dB HL ≤ PTA AC