Audiological Findings in Osteogenesis Imperfecta

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Abstract

Background: Osteogenesis imperfecta (OI) is an inherited bone and connective tissue disorder associated with the lifelong occurrence of frequent fractures following even mild trauma. Hearing loss is frequently reported in patients with OI.

Purpose: This investigation is a retrospective study of measurements of tympanometry, acoustic reflexes, and transient evoked otoacoustic emissions in a sample of patients with OI grouped according to age. The purpose of the study was to examine the relationship between the type of OI, age, and audiological findings in a sample of individuals with OI.

Research Design: The study examined the correlation between audiometric measures, hearing loss of all types, and type of OI.

Study Sample: Forty-one patients with OI were included in the study. The patients were divided into two groups for analysis: one group less than 20 years of age (n = 21) and the other group aged 20 and over (n = 20).

Results: Hearing loss of all etiologies was observed in 62% of ears. Sensorineural or mixed hearing loss was observed in 41% and conductive hearing loss in 21% of ears. Results indicate that the younger patients with OI were subject to a greater risk of middle ear dysfunction associated with otitis media than is typical for children of comparable age. Tympanometric abnormalities associated with ossicular dysfunction were more often found in the older age group of patients. Hearing loss of all types was more prevalent in the older group of patients (88%) than in the younger patient group (38%).

Conclusions: Hearing loss was not uncommon regardless of age. Therefore, close audiological monitoring of patients with OI is recommended across the age spectrum.

Key Words: Acoustic reflex, osteogenesis imperfecta, transient evoked otoacoustic emissions, tympanometry

Abbreviations: CHOI = characteristic of osteogenesis imperfecta; OI = osteogenesis imperfecta; OME = otitis media with effusion; TEOAEs = transient evoked otoacoustic emissions

Sumario

Antecedentes: La osteogénesis imperfecta (OI) es un trastorno heredado del hueso y del tejido conectivo asociado con la presencia de fracturas durante la vida aún con traumas leves. Los trastornos auditivos están frecuentemente reportados con la OI.

Propósito: Esta investigación es un estudio retrospectivo de mediciones de timpanometría, reflejos acústicos y emisiones otoacústicas evocadas por transitorios, en una muestra de pacientes con OI agrupados de acuerdo a la edad. El propósito del estudio fue examinar la relación entre el tipo de OI, la edad, y los hallazgos audiológicos en una muestra de individuos con OI.

Diseño de la Investigación: El estudio examinó la correlación entre las medidas audiométricas, la pérdida auditiva de todos los tipos y el tipo de OI.

Muestra del Estudio: Cuarenta y un pacientes con OI fueron incluidos en el estudio. Los pacientes se dividieron en dos grupos para el análisis: un grupo de menos de 20 años de edad (n = 21) y el otro grupo por encima de los 20 años (n = 20).

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Resultados: La hipoacusia de todas las etiologías fue observada en 62% de los oídos. Se observaron pérdida auditivas sensorineurales o mixtas en 41% y conductivas en 21% de los oídos. Los resultados indican que los pacientes más jóvenes con OI estaban sujetos a un mayor riesgo de disfunción del oído medio asociado con otitis media de lo que es típico para niños de edad comparable. Las anormalidades timpanométricas asociadas con una disfunción oscicular se encontraron más a menudo en el grupo más viejo de pacientes. Las hipoacusias de todos los tipos fueron más prevalentes en el grupo más viejo de pacientes (88%) que en el grupo más joven (38%).

Conclusiones: La hipoacusia no fue poco común sin importar la edad. Por tanto, se recomienda un monitoreo audiológico de los pacientes con OI en todo el espectro de edades.

Palabras Clave: Reflejo acústico, osteogénesis imperfecta, emisiones otoacústicas evocadas por transitorios, timpanometría

Abreviaturas: CHOI = características de la osteogénesis imperfecta; OI = osteogénesis imperfecta; OME = otitis media con efusión; TEOAE = emisiones otoacústicas evocadas por transitorios

O steogenesis imperfecta (OI) is an inherited bone and connective tissue disorder associated with the lifelong occurrence of frequent fractures following even mild trauma. It is a heterogeneous disorder in terms of both genetic and clinical characteristics. Secondary deformities of the extremities, spine, and skull as well as short stature are also commonly observed (Byers and Cole, 2002). Dentinogenesis imperfecta (a similar disorder of the teeth) is also commonly found in association with OI. OI is estimated to occur with a frequency of 4.9–5.0 per 100,000 (Pedersen, 1984; Kuurila et al, 2002) on the basis of population surveys in Finland and large sample surveys in the United Kingdom. OI is characterized by deficiencies in the synthesis of type 1 collagen and is associated with skeletal abnormalities as well as hearing loss (Kuurila et al, 2002). A wide variety of mutations have been reported in the COL1A1 (collagen, type 1, alpha 1) and COL1A2 (collagen, type 1, alpha 2) genes, which explains, in part, the significant clinical variety observed in OI (Hartikka et al, 2004). Recently, mutations involving the genes CRTAP (cartilage associated protein) and LEPRE1 (leucine proline-enriched proteoglycan [leprecan] 1, a growth suppressing gene), which modify type I collagen synthesis, have been reported in severe and lethal cases (Cabral et al, 2007). OI was initially classified into four major types on the basis of clinical, radiological, and genetic criteria developed by Sillence (Sillence and Rimoin, 1978) and later modified by the International Working Group on Constitutional Diseases of Bone (1998). A more recent classification system that includes new OI types is shown in Table 1.

Hearing loss varies with the type of OI and is most common in Type I OI and rarely reported in Type IV OI (Sillence, 1981). OI may be associated with neurological complications in rare cases such as skull fractures, seizure disorders, and brainstem compression secondary to basilar invagination (Charnas and Marini, 1993)

It is widely reported that conductive hearing loss in OI is found in younger patients whereas sensorineural hearing loss is found more in older patients (Quisling et al, 1979; Pedersen, 1984; Garretsen et al, 1997; Kuurila et al, 2002). The likelihood of hearing loss, reported by some investigators to be infrequent until the second or third decade of life, increases with advancing age (Quisling et al, 1979; Riedner et al, 1980; Pedersen, 1984). However, other investigators have reported that hearing loss in younger patients with OI is not uncommon (Kuurila et al, 2002; Imani et al, 2003). Typically the hearing loss associated with OI is viewed as initially conductive in nature and progressive (Pedersen, 1984). However, on the basis of a nationwide survey of OI in Finland, mixed or sensorineural hearing loss may be observed at any age (Kuurila et al, 2002).

Table 1. Types of Osteogenesis Imperfecta

Type	Inheritance	Clinical	Mutations
I	AD	Mild, blue sclerae, fractures with little or no deformity, hearing loss, DI	Type I collagen COL1A1, COL1A2
II	AD, AR	Lethal, pulmonary insufficiency, beaded ribs, rhizomelic, hearing loss	Type I collagen COL1A1, COL1A2
III	AD, AR	Progressive deforming, Intrauterine fractures, deformed limbs, scoliosis, white or blue sclerae, hearing loss, DI	Type I collagen COL1A1, COL1A2
IV	AD	Moderately severe, limb deformity, sclerae blue early and lighten with age, scoliosis	Type I collagen COL1A1, COL1A2
V	AD	Variable phenotype like IV, hyperplastic callus, dislocated radial head, calcified interosseous membrane	Unknown
VI	Unknown	More fractures than IV, mineralization defect on biopsy, vertebral fractures, no DI	Unknown
VII	AD	First Nations family, Quebec, Congenital fractures, white sclerae, severe rhizomelia	CRTAP (prolyl-3 hydroxylation)

Note: AD = autosomal dominant; AR = autosomal recessive.
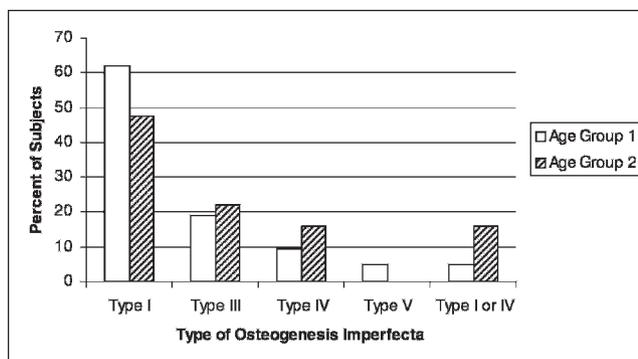
Figure 1. Type of osteogenesis imperfecta (in %) for Age Group 1 and Age Group 2.

When sensorineural hearing loss is found in children, it is typically found in Type I OI (Kuurila et al, 2002).

While the measurement of otoacoustic emissions has been found to support the presence of a conductive component in ears with otosclerosis (Probst, 2007) and other forms of conductive pathology (Zhao et al, 2003), there are no studies in the literature in patients with OI that have included measurement of otoacoustic emissions. This investigation was a retrospective study of measurements of tympanometry, acoustic reflexes, and transient evoked otoacoustic emissions in a sample of patients with OI grouped according to age.

METHODS

Subjects

The subjects were identified retrospectively by the diagnosis code database at Kennedy Krieger Institute in Baltimore, Maryland. The Johns Hopkins University School of Medicine and Gallaudet University Institutional Review Boards granted approval for the study. The 41 patients, 26 female and 15 male, were seen by both the OI clinic and the audiology clinic between 1997 and 2007 for complete exams. Patients at the time of testing ranged in age from 2.67 years to 68 years with a mean of 26.54 years and a standard deviation of 19.55 years. Patients were divided into two groups on the basis of age. Patients in Group 1 were less than 20 years of age, and patients in Group 2 were 20 years of age and over. There were 21 patients ranging in age from 2.67 to 15.33 in Group 1 (mean age = 9.87; SD = 4.33) and 20 patients ranging in age from 21 to 68 (mean age = 44.05; SD = 12.44) in Group 2. The distribution of type of OI in the total sample and for each age group is shown in Figure 1. The distribution of OI types was very similar across age groups. No cases of Type II OI were present in the sample as Type II OI is lethal. No cases of Types VI and VII, which have been reported only from Canada in limited numbers, are included in this series. "Type I and IV" is called such because in some patients we could not differentiate severe Type I from a mild Type IV OI.

Type IV OI is a very heterogeneous group lying between relatively mild Type I and the more severe Type III OI.

Audiometric Data

Pure-Tone Audiometry

Auditory sensitivity was assessed utilizing conventional audiometric techniques for the majority of patients; for four patients, conditioned play audiometry was utilized. Measures of speech audiometry were obtained utilizing developmentally appropriate audiometric techniques.

For purposes of hearing classification, sensorineural hearing loss was defined as thresholds greater than 20 dB HL (ANSI, 1989) for one or more frequencies from 250 to 8000 Hz with no air-bone gap greater than 10 dB HL from 250 to 4000 Hz. When no significant air-bone gaps were present from 250 to 4000 Hz and thresholds were markedly elevated in only the 6000 to 8000 Hz frequency region, the audiograms were classified as CHOI (characteristic of osteogenesis imperfecta) in accordance with an earlier study by one of the present authors (Shapiro et al, 1982). Conductive hearing loss was defined as present when air conduction thresholds exceeded 20 dB HL and there was at least one air-bone gap greater than 10 dB HL with bone condition thresholds better than 20 dB HL from 250 to 4000 Hz. Mixed hearing loss was defined as thresholds greater than 20 dB HL with bone conduction thresholds greater than 15 dB HL with air-bone gaps greater than 10 dB HL for at least one frequency from 250 to 4000 Hz.

Acoustic Immittance

Tympanograms were obtained with an acoustic admittance measurement unit. The GSI TympStar and the Madsen Zodiac were both utilized. The probe frequency was 226 Hz. The air pressure was swept in the ear canal from +200 to −300 daPa. Compensated static admittance (Peak Y_{tm} [peak static acoustic admittance] in mmho), tympanic peak pressure (daPa), and tympanometric width (daPa) were measured. Tympanograms were classified into Types (A, A_D, A_S, B, and C) as described by Jerger (1970). Acoustic reflex measurements were also obtained for ipsilateral stimulation of both ears with pure-tone stimuli from 500 to 4000 Hz. Acoustic reflexes were defined as abnormal if two or more reflex thresholds were elevated (greater than 100 dB HL) or absent.

Otoacoustic Emissions

Measurements of transient evoked otoacoustic emissions (TEOAEs) were obtained utilizing two measurement systems with versions of the Otodynamics
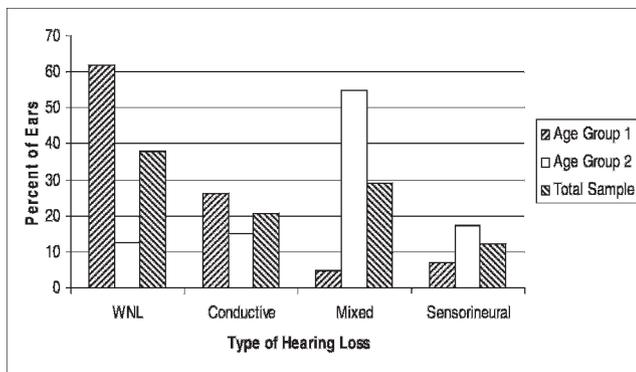
Figure 2. Type of hearing loss (in %) for Age Group 1 and Age Group 2.

software. This was the case because the patients were assessed in two different locations over the course of several years. The ILO88DP and the Madsen Capella measurement systems were utilized. When TEOAE measurements were undertaken with the ILO88DP system, the QUICK SCREEN option (Otodynamics, Version 5.6) was employed. The Fast Screen option was utilized for measurements undertaken with the Madsen Capella measurement system. For both systems, the correlation within five half octave bands from 1000 to 4000 Hz was utilized in response determination. TEOAEs were defined as abnormal if the correlation in two or more of the frequency bands was less than 70%.

RESULTS

Pure-Tone Audiometry

In the overall sample, 62% of the ears had a hearing loss ranging from mild to profound. Hearing loss of all types was more common in the ears of Group 2 (88%) than in Group 1 (38%). The type of hearing losses found in the sample of OI patients are shown in Figure 2 for Group 1, Group 2, and for the total sample. Mixed hearing loss was found in 29% of ears for the total sample. Mixed hearing loss was found in 55% of patients in Group 2 but in only 5% of Group 1. Conductive hearing loss was found in 21% and sensorineural hearing loss in 12% of ears for the total sample.

Acoustic Immittance

As shown in Figure 3, abnormal tympanograms were found in 43% of the younger age group with OI and 33% of the older patients. For the younger age group, the most prevalent abnormal tympanometric types observed collectively (A_S, B, and C) were suggestive of middle ear effusion whereas for the older age group, the Type A_D pattern was the most common abnormal finding. The older group of OI patients failed acoustic reflex testing with greater frequency (57%)
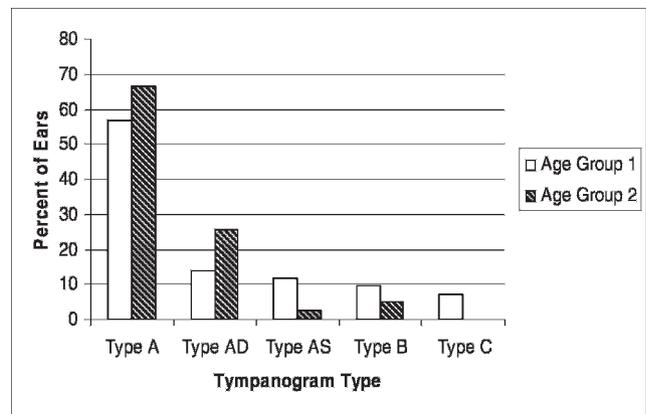
Figure 3. Percent of ears with tympanogram Type A, Type A_D, Type A_S, Type B, and Type C for Age Group 1 and Age Group 2.

than the younger patients (31%). This difference was significant using the Fisher exact test ($p < .04$).

Otoacoustic Emissions

The older patients with OI failed TEOAEs (63%) with significantly greater frequency ($p < .004$) using the Fisher exact test than the younger age group of OI patients (29%).

Relation between Abnormal Test Findings and Hearing Loss

As shown in Figure 4, tympanometry was abnormal in 65% of ears with conductive hearing loss and in 48% of ears with mixed hearing loss. Acoustic reflex abnormalities were present in 86% of ears with conductive hearing loss and 65% of ears with mixed hearing loss. Abnormal TEOAEs were present in 71% of ears with conductive hearing loss and 73% of ears with mixed hearing loss but only 40% of ears with
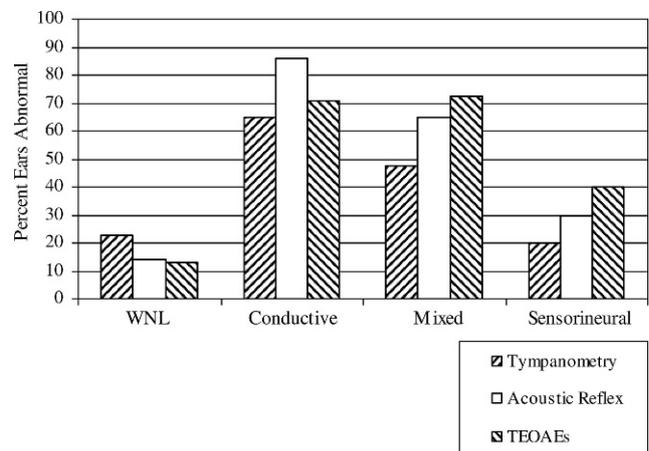
Figure 4. Percent of abnormal findings for tympanometry, acoustic reflexes, and TEOAEs in ears with normal hearing and ears with hearing loss of all types.

Table 2. Performance of Tympanometry, Acoustic Reflex Testing, and Transient Evoked Otoacoustic Emissions in Patients with All Types of Hearing Loss

	Tympanometry	Acoustic Reflex	TEOAEs
Normal Hearing	23	14	13
Hearing Loss	48	64	65
Kappa	0.23	0.46	0.49

sensorineural hearing loss. The Kappa statistic (Agresti, 1990) was utilized to assess the degree of agreement between the diagnosis of hearing loss and the presence of abnormal test results. As shown in Table 2, there was a moderate relationship between outcome of TEOAE and acoustic reflex testing and the presence of hearing loss of all types. However, there was a relatively weak relationship between tympanometric outcome and the presence of hearing loss of all types.

DISCUSSION

Hearing loss is relatively common in OI with 62% of ears found to have hearing loss ranging from mild to profound. Some studies have reported a slightly lower percentage of hearing loss in ears of patients with OI (50%) (Riedner et al, 1980; Cox and Simmons, 1982). Other studies have reported a higher prevalence of hearing loss (65–72%) compared to the present investigation (Pedersen, 1984; Stewart and O'Reilly, 1989). Methodological or definitional differences may account for the varying results across studies (Imani et al, 2003). Some investigators have excluded cases of conductive hearing loss believed to be secondary to otitis media with effusion (OME) in younger patients with OI (Stewart and O'Reilly, 1989; Garretsen et al, 1997). This practice may lead to underestimation of the prevalence of hearing loss in OI as well as a failure to recognize the possibility of an increased susceptibility to OME in patients with OI perhaps as a consequence of cranial molding or deformation (Imani et al, 2003). Subject selection issues are also a consideration. When only Type I OI patients are selected for study, the prevalence of hearing loss of all types has been as high as 91% (Garretsen et al, 1997).

Tympanometric abnormalities were not associated to a significant degree with the presence of hearing loss of all types. Only 65% of ears with conductive hearing loss and 48% of ears with mixed hearing loss were found to have abnormal tympanograms. In patients with OI it is possible that the presence of multiple otologic pathologies may confuse the interpretation of tympanometric findings; pathology contributing to high admittance may be masked by pathology resulting in reduced admittance of the tympanic membrane/middle ear system (Feldman, 1974; Rawool and Harrington, 2007). An examination of tympanogram types did indicate that the most prevalent abnormal tympanometric types observed (A_S, B, and C) for the younger age group were consistent with the presence of middle ear effusion whereas for the older age group, the Type A_D pattern possibly suggestive of ossicular discontinuity was the most common abnormal finding. The use of only a low-frequency probe tone may have contributed to the poor performance of tympanometry in the present study. Additional measures such as determination of resonant frequency of the middle ear may improve the utility of tympanometry in patients with OI (Rawool and Harrington, 2007). TEOAEs were typically absent in the present study when a hearing loss exceeded 30 dB as has been reported elsewhere (Prieve et al, 1993; Harrison and Norton, 1999). However, as also previously reported (Harrison and Norton, 1999), poor performance for TEOAEs was observed for low-frequency hearing loss. Poor performance was also observed for hearing loss restricted to the 6000–8000 Hz frequency region in this study.

In the present investigation, sensorineural hearing loss was present in 12% of ears, conductive hearing loss in 21%, and mixed hearing loss in 29% of ears. As has been reported by others (Kuurila et al, 2002; Imani et al, 2003), sensorineural hearing loss was present in the younger age group consisting of children (mean age = 9.87; SD = 4.33) in the present investigation and was found only in association with Type I OI. The representation of hearing loss progression in OI, conductive hearing loss progressing to later onset mixed or sensorineural hearing loss, is not universally accepted. Some authors have indicated that sensorineural loss as the initial presenting etiology is commonly found in OI (Shapiro et al, 1982; Imani et al, 2003). The observation of hearing loss in some patients with OI at 6000–8000 Hz has been viewed as an indication of early sensorineural hearing loss by some authors (Shapiro et al, 1982; Imani et al, 2003). This supposed characteristic configuration of hearing loss in OI has been labeled *CHOI*. The CHOI hearing loss type is viewed as an early indicator for progression of hearing loss to more severe levels in the high frequency region with additional involvement of the lower frequencies over time (Shapiro et al, 1982). However, other investigators have claimed that the impairment in the high-frequency region in older patients with OI appears to follow the age-related progression of hearing loss seen in large scale hearing surveys (Pedersen, 1984). There is some limited evidence supporting the view of an initial presentation of sensorineural hearing loss in OI. Progression of a hearing loss was observed from sensorineural to mixed origin in a 24-year-old followed by Alkadhi et al (2004) over a two-year interval. The patient was found to have bandlike, undermineralized pericochlear areas at age 24 that were later found to have to progressed to the promontory and round window niche two years later when the initial conductive component was identified. No longitudinal studies in groups of patients with OI are available to definitively resolve the issue.

The CHOI audiometric configuration was observed in only 5% of ears in this investigation. When the CHOI pattern was found, it was always found in the older age group. Findings in the present investigation indicate that while sensorineural hearing loss can occur as the initial presentation of hearing loss in OI, the sensorineural component is not necessarily restricted to the 6000–8000 Hz frequency region. Examination of the audiograms in the present investigation revealed a variety of audiometric types including low- or mid-frequency sensorineural hearing loss in the absence of significant hearing loss in the 6000–8000 Hz frequency region.

The use of bone conduction thresholds in determination of hearing loss etiology is problematic as bone conduction thresholds are known to be elevated in otosclerosis in the 2000 Hz region. Immobility of the stapes footplate with consequent mechanical restriction of the perilymph may alter cochlear function sufficiently to elevate bone conduction thresholds (Hall et al, 1993). In contrast, bone conduction thresholds may be unusually low in the frequency region below 2000 Hz in patients with dehiscence of the superior semicircular canal (Probst, 2007). Air-bone gaps in the low-frequency region are also observed in patients with large vestibular aqueduct syndrome (Nakashima et al, 2000). In such cases, an apparent conductive component would not be expected to necessarily be supported by abnormalities in other audiologic measures such as low-frequency tympanometry as utilized in the present investigation.

The etiology of sensorineural hearing loss in OI has not been definitively determined. Patients with OI are at greater risk for skull fractures that are associated with hearing loss. Autopsy findings have shown hair cell loss, abnormalities of the tectorial membrane, perilymph hemorrhage, atrophy and calcification of the stria vascularis in OI (Bergstrom, 1981). CT scans in OI have revealed under mineralization of the optic capsule with involvement of the cochlea, semicircular canals, the distal internal auditory canal, and oval window in an individual with a moderately severe hearing loss of mixed origin (Heimert et al, 2002).

Hearing loss of all types was very common in the older age group with 87% of ears having some degree of hearing loss. In contrast, hearing loss of all types was less common in the younger age group but was still present in 38% of ears in the younger patients. Previous studies of hearing loss in the pediatric population with OI have reported widely divergent findings that have ranged from a prevalence of 9.1% (Kuurila et al, 2000) to 77.3% (Imani et al, 2003). The later study included patients with OME, history of skull fracture, and neonatal meningitis in the sample studied. Studies have also differed as to the definition of hearing loss. While inclusion of patients with OME and other etiologies apparently not directly related to OI has been challenged by some investigators (Kuurila and Grenman, 2004), in the present investigation as in others (Imani et al, 2003), no a priori assumptions were made as to whether factors present in the medical history were not related to the complex of symptoms experienced by patients with OI. Consequently, the presence of OME, history of head trauma, or bacterial meningitis were not exclusion criteria in the present investigation as long as the patient presented with the diagnosis of OI. The Imani et al (2003) study also included patients with OME, history of skull fracture, and neonatal meningitis in the sample studied.

Conductive hearing loss is also commonly found as the initial manifestation of hearing loss in OI. Pediatric patients with OI may initially present with conductive hearing loss associated with otitis media. In the present investigation and in others (Imani et al, 2003), findings suggest the possibility of increased susceptibility of pediatric patients with OI to OME. Tympanometric abnormalities consistent with the presence of middle ear effusion in the younger age group were common with 43% of the sample failing tympanometry. Failure rates for tympanometry in preschool and school-age children are more typically in the range of 8.6% to 13.5% (Taylor and Brooks, 2000; Driscoll et al, 2001), suggesting a higher rate of failure for tympanometry in OI than in the general preschool and school-age population. A high incidence of otitis media with effusion in younger patients with OI has been reported and has been attributed to the presence of craniofacial dysmorphism in OI (Imani et al, 2003). A high-frequency of OME is also commonly observed in other syndromes characterized by morphological abnormalities of the temporal bone (Shohat et al, 1993).

The cause of conductive impairments in OI is often associated with footplate fixation although fractures of the crura are not uncommon (Albahnasawy et al, 2001). While it has been noted that features of hearing loss in OI such as ossicular involvement and hearing loss progression are ostensibly similar to those found in otosclerosis (Pedersen, 1984), the two disorders are biochemically divergent (Holdsworth et al, 1973). On the basis of histopathological data, it has been suggested that OI is a generalized disorder of the bone and connective tissue whereas otosclerosis is more commonly a localized disease of the temporal bone (Pedersen et al, 1985). In addition, sensorineural hearing loss is more commonly reported in OI than in otosclerosis and at earlier ages (Kuurila et al, 2002).

Findings in this study indicate that hearing loss is associated with OI across the age spectrum. Although the frequency of occurrence of hearing loss is greater in older patients with OI, pediatric patients with OI are also at significant risk for hearing loss, suggesting the need for audiological monitoring of children as well as adults with OI.

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