Van der Hoeve Syndrome and Stapes Surgery: Case Reports and a Review

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Abstract: Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones. People with this condition have bones that break easily, often from mild trauma or with no apparent cause.

There are at least eight recognized forms of osteogenesis imperfecta, designated type I through type VIII. The classic triad of conductive hearing loss, spontaneous fracture and blue sclera is known as Van der Hoeve Syndrome. The aim of the study is to evaluate some case reports with Van der Hoeve Syndrome treated with stapes surgery and to make a review of this syndrome.

In the period from 2001 to 2009 4 Caucasian patients affected with Van der Hoeve Syndrome underwent stapes surgery. Totally 6 ears were treated.

According to our results, even though the number of patients is limited, stapes surgery in patients with Van der Hoeve syndrome has to be considered a valuable technique in improving hearing if performed by an experienced surgeon.

Stapes surgery is successful in resolving the conductive hearing loss in OI patients, even in the long term. Moreover it could reduce the progression of sensorineural hearing impairment.

The improvement seems to last in time, even though more studies are necessary.

Keywords: Osteogenesis imperfecta, hearing loss, otosclerosis, blue sclera, stapes surgery.

INTRODUCTION

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones. The term "osteogenesis imperfecta" means imperfect bone formation.

People with this condition have bones that break easily, often from mild trauma or with no apparent cause. Multiple fractures are common, and in severe cases, can occur even before birth. Milder cases may involve only a few fractures over a person's lifetime. The incidence of osteogenesis imperfecta is estimated to be 1 in 20.000 to 1 in 30.000 newborns [1].

In general, the disease is inherited in an autosomal dominant pattern. Sometimes, it is the result from a recessive inheritance pattern, from a spontaneous mutation or from parental mozaicism [2]. Casual mutations for OI involve either the COL1A1 gene or the COL1A2 gene, located on the chromosome 17 and chromosome 7 respectively. These genes encode for the pro-α-1 and the pro-α-2 chains of type I procollagen. Type I collagen forms an important structural protein in the formation of the extracellular matrix of different organs like bone, blood vessels, skin, and other fibrous tissues. Mutations in the procollagen genes result in either a reduced production of this protein or the production of an abnormal type I collagen. Both quantitative and qualitative disturbed type I collagen synthesis can be responsible for the symptoms and signs of OI.

There are at least eight recognized forms of osteogenesis imperfecta, designated type I through type VIII [3]. The types can be distinguished by their signs and symptoms, although their characteristic features overlap. Type I is the mildest form of osteogenesis imperfecta and type II is the most severe; other types of this condition have signs and symptoms that fall somewhere between these two extremes. Increasingly, genetic factors are used to define the different forms of osteogenesis imperfecta.

The milder forms of osteogenesis imperfecta, including type I, are characterized by bone fractures during childhood and adolescence that often result from minor trauma. Fractures occur less frequently in adulthood. People with mild forms of the condition typically have a blue or grey tint of the part of the eye that is usually white (the sclera), and may develop hearing loss in adulthood. Affected individuals are usually of normal or near normal height.

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Table 1: Enrolled Patients: Characteristics and Audiometric Levels Before Surgery

Patients, ear, sex	Age	AC	BC	ABG
DG, f, r	50	44.4	18.1	26.3
DG, f, l	50	45.0	13.1	31.9
CL, m, l	39	46.9	21.3	25.6
BE, f, r	60	45.6	15.0	30.6
BG,m, l	32	38.8	16.9	21.9
BG,m, r	32	37.8	15.9	21.9

f: female; m: male; r: right; l: left.
AC: Air conduction mean threshold obtained at 0.5, 1.0, 2.0 and 4.0 Hz expressed in dB.
BC: Bone conduction mean threshold obtained at 0.5, 1.0, 2.0 and 4.0 Hz expressed in dB.
ABG: Air-bone gap.

Other types of osteogenesis imperfecta are more severe, causing frequent bone fractures that may begin before birth and result from little or no trauma. Additional features of these conditions can include blue sclera, short stature, hearing loss, respiratory problems, and a disorder of tooth development called dentinogenesis imperfecta. The most severe forms of osteogenesis imperfecta, particularly type II, can include an abnormally small, fragile rib cage and underdeveloped lungs. Infants with these abnormalities have life-threatening problems with breathing and often die shortly after birth.

The classic triad of conductive hearing loss, spontaneous fracture and blue sclera, is known as Van der Hoeve and de Klein syndrome [4].

The aim of the study is to evaluate some case reports with Van der Hoeve Syndrome treated with stapes surgery and to make a review of this syndrome.

MATERIAL AND METHODS

In the period from 2001 to 2009 4 Caucasian patients (2 female, 2 male) underwent stapes surgery performed by the same surgeon. Two patients were treated for both ears. Totally 6 ears were treated (Table **1**) (Figure **1**).

Informed consent was obtained from all the patients. All of them agreed with molecular-genetic confirmation of the clinical diagnosis of OI by mutation analysis of DNA.

Micro-otoscopy and an extensive audiological test battery consisting of pure tone audiometry, tympanometry and stapedial reflex were performed.

CT was performed in all the patients (Figure **2**).

All the patient underwent monolateral stapes surgery that consisted in incudo-stapedotomy with the

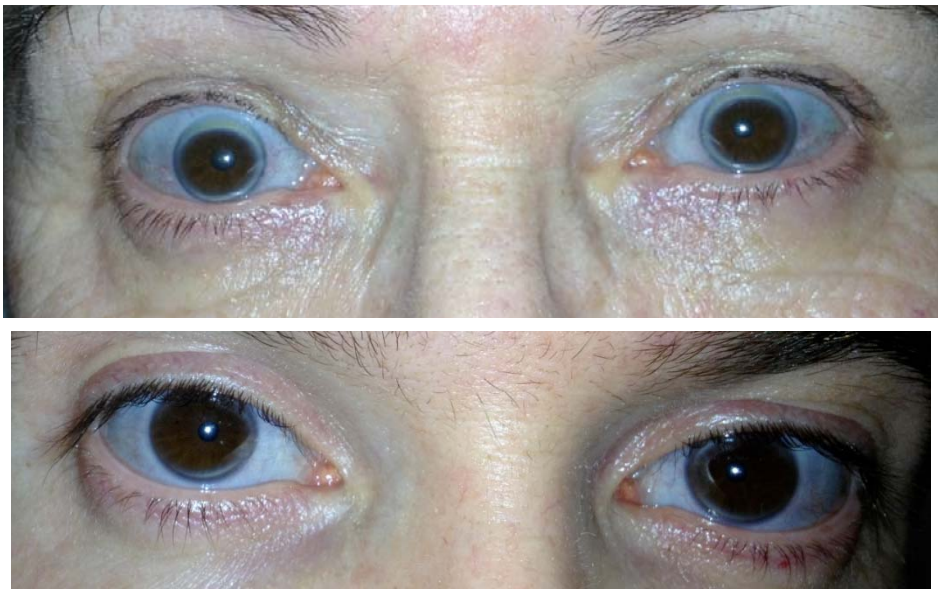

Figure 1: patients with typical blue sclerae.

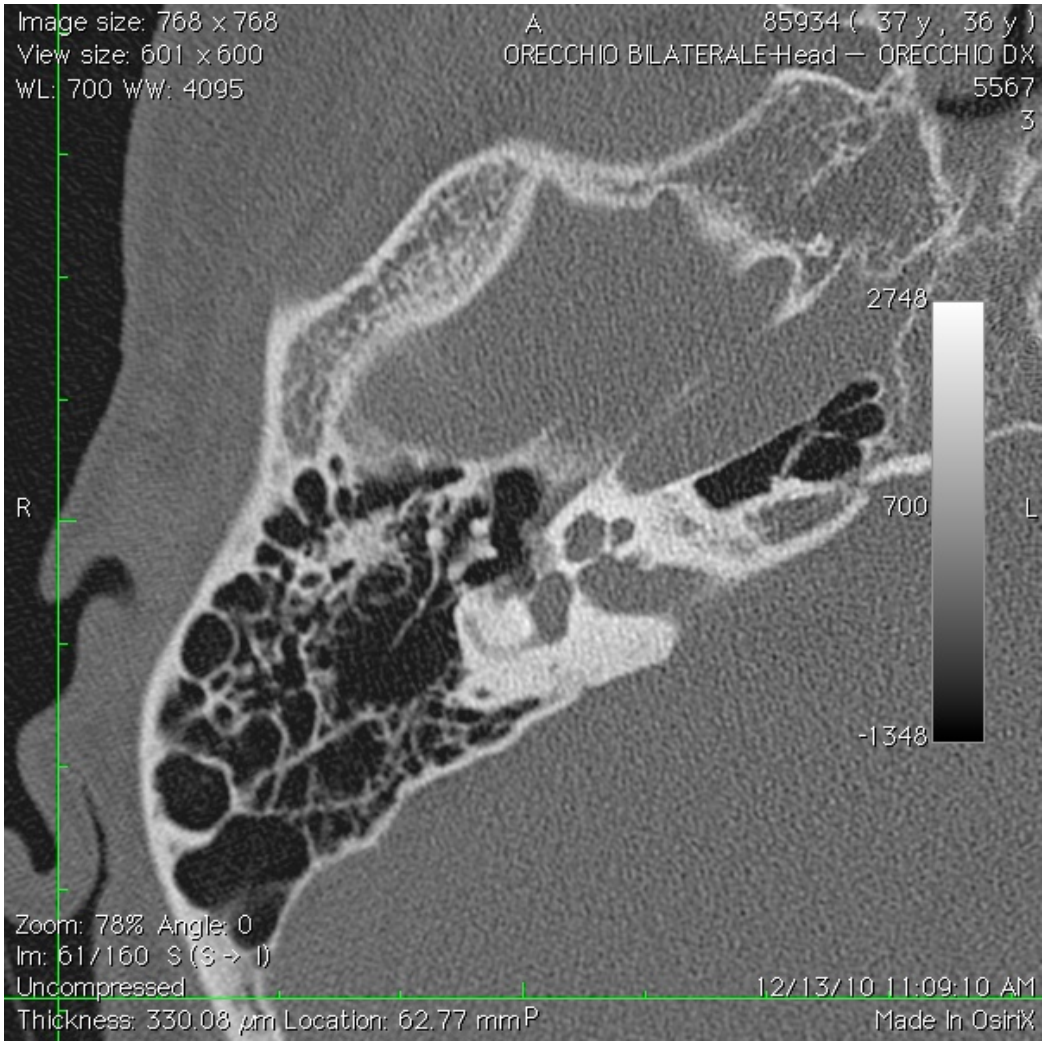

Figure 2: CT of a patient with Van der Hoeve Syndrome, right ear: as it happens in otosclerosis no particular findings are detected.

inversion of surgical steps and using a Teflon platinum wire prostheses.

Post-operative audiometry was performed at 6 weeks, 6 months, 1 year and 2 years.

RESULTS

In all the patients the clinical diagnosis of Van der Hoeve syndrome was confirmed by DNA analysis: the underlaying genetic mutations was located in the COL1A1 gene 2 ears suffered from pure conductive hearing loss, 4 ears had a mixed hearing impairment.

For each ear we evaluated the mean Air conduction, bone conduction and air bone gap before the surgical operation, in the short and long term (immediately, 6 months and 2 years) (Figure **3**).

Short–term post-operative audiometric results showed an improvement in all ears, the hearing gain for AC being larger than 20 dB. Long-term follow-up showed an improvement going from 3.8 to 15 dB.

DISCUSSION

In 1912 Adair Dighton [5] described a family of fourteen people, comprising four generations, nine of whom showed blue sclera, and of these, one, a woman, aged 22, had become deaf after a confinement. The deafness was described as “nerve deafness”, but may well have been otosclerosis in which the onset of internal ear symptoms preceded that of middle-ear deafness.

In 1916, Van der Hoeve and de Klein [6] definitely associated the three members of the triad and showed that the hearing loss tended to conform clinically to the type of otosclerosis. Since then many studies have been conducted.

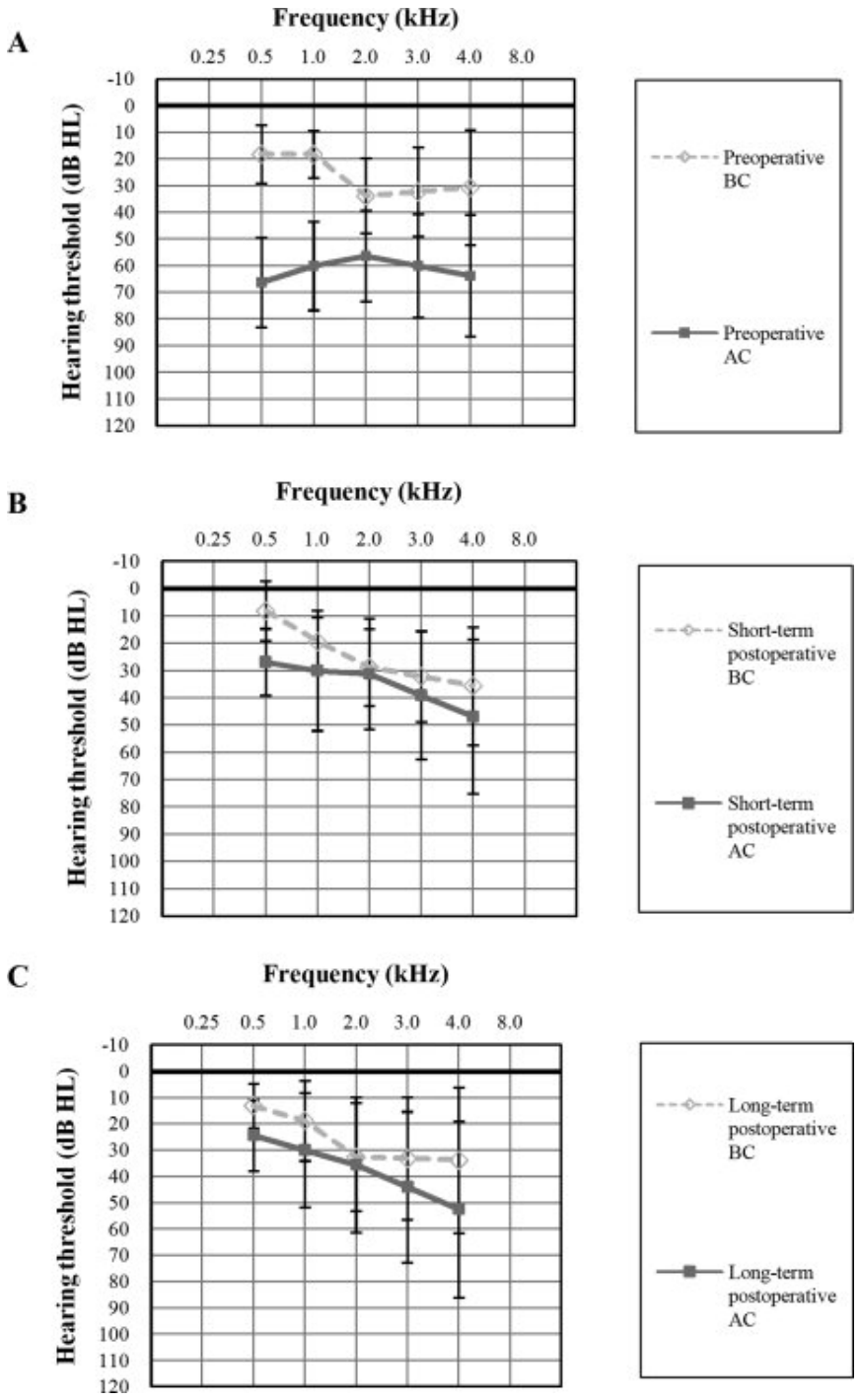

Figure 3: the mean Air conduction (AC) and bone conduction (BC) before surgical operation, in the short and long term (immediately, 6 months and 2 years) (Figure **3**).

The prevalence of hearing loss differs considerably in literature and is reported to vary from 26% to 78% [7-9]. Hearing impairment in OI usually appears in the late-second to early-third decade of life [10] and is mostly of the mixed type; however, a pure conductive or a pure sensorineural hearing impairment can occur [11]. Conductive hearing loss is most often related to fixation of the stapes footplate, but can also be due to ossicular discontinuity because of the aplasia or fractures of the stapedial crura. Sensorineural hearing loss in patients with OI usually results from atrophy of the cochlear hair cells and the stria vascularis, and from anomalous bone formation in and around the cochlea [12].

Our patients suffered from pure conductive hearing loss (2 ears) and mixed hearing loss (4 ears). Our intra-operative findings with stapes surgery confirm the

middle ear pathology typical for OI as reported by others [13-14].

The most common feature was the fixation of the footplates that was present in all our cases. In two of them we found the fracture of the stapes crura that was atrophic in one patient and thick in 3 of them. Only in one case we found an hypervascularization of the mucosa that gave rise to excessive bleeding that was successfully managed.

OI is histopathologically characterized by thickened and undermineralized bone: the pathologic changes in the temporal bone are qualitatively similar to those occurring in the peripheral skeleton [15]. There is a deficient bone, as indicated by the presence of numerous and large vascular spaces and lack of bone development causing brittle bony mastoid portions [16]. These features can be detected with CT and MRI. All patients of our study underwent CT that showed typical alterations.

OI and otosclerosis share many similar histologic and radiologic features, and their relationship has been controversially regarded in the literature, although biochemical data demonstrated dissimilar protein and enzyme concentrations in these two entities [17]. Histological analysis showed that otosclerosis also can be distinguished morphologically, because OI involves all three layers of the otic capsule (endosteum, endochondral layer and periosteum), whereas otosclerosis is limited to endochondral layer [17]. At CT and MR imaging, the demineralization of the otic capsule in OI is remarkably similar to that occurring in otosclerosis [18]. OI, however, is a generalized bone disorder, whereas otosclorosis is a localized disease of the petrous bone. Furthermore, the severity of the involvement of the bony labyrinth appears to be greater in OI than in otosclerosis [18]. The onset of hearing loss is earlier in OI than in otosclerosis, occurring most commonly during the 2nd and 3rd decades of life.

In OI moreover, sensorineural hearing loss is more common than in otosclerosis and results from microfractures and reaparative vascular and fibrous tissue around the cochlea.

Differential diagnosis must be done also with Paget disease and otosyphilis.

In Paget disease involvement of the temporal bone is associated with changes of the skull [18]. CT shows diffuse demineralization of the entire petrous bone in a characteristic washed-out appearance.

In otosyphilis the demineralization is typically accompanied by systemic manifestations of syphilis and by the demineralization of the ossicular chain which has never been reported in OI.

Although stapes surgery has long been a generally accepted technique to improve hearing in otosclerosis patients, more controversies remain concerning the results of this intervention in OI patients, especially in the long term, because OI related hearing loss is known to deteriorate with increasing age, predominantly because of the progression of the sensorineural component.

During the last decades some reports on audiometric results of stapes surgery in OI patients have been published [19,20], but non clinical review has been made in Italy.

According to our results, even though the number of patients is limited, stapes surgery in patients with Van der Hoeve syndrome has to be considered a valuable technique in improving hearing if performed by an experienced surgeon.

In general stapes surgery is successful in resolving the conductive hearing loss in OI patients, even in the long term. Moreover it could reduce the progression of sensorineural hearing impairment.

Stapes surgery is not very different in OI patients than otosclerosis patients and it doesn't report more difficulties.

The improvement seems to last in time, even though more studies are necessary.

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