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Etiopathogenesis of Otosclerosis

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Key Words
Otosclerosis · Collagen · Heredity · Measles virus

Abstract
Otosclerosis is a frequent cause of nonsyndromic hearing loss which affects exclusively the human temporal bone. Various etiopathogenetic hypotheses have been proposed. The major hypotheses considered are genetic factors, immunologic factors and viral infection. Since the familial incidence of otosclerosis is known a recent genetic analysis has given evidence of three otosclerosis genes (OTSC1–3). Mutations in the collagen gene COL1A1 have been found in one large family with several cases of otosclerosis. Concerning an immunologic etiopathogenetic process, the presence of serum antibodies against collagen II and IX in patients with otosclerosis confirms the hypothesis of a collagen autoimmune mechanism. Finally as a possible cause of this chronic inflammatory disease morphologic and biochemical investigations have revealed a measles virus association. In conclusion, various etiopathogenetic factors may contribute to the genesis of otosclerosis.

Introduction

Otosclerosis is a peculiar chronic disease which affects exclusively the human osseous labyrinth. It is Valsalva [1] who has been credited with having been the first to connect hearing loss to stapes footplate fixation. Toynbee [2] dissected temporal bones of patients with hearing loss and he described a fixation of the stapes in 35 out of 1,659 samples. Von Tröltsch [3] is considered to have coined the term otosclerosis because of his believing that middle ear sclerosis leads to a fixation of the stapes. The first detailed histopathologic description of otosclerosis was published by Politzer [4]. The term 'otospongiosis' was proposed by Siebenmann [5] and otospongiosis is currently used in French meaning otosclerosis. Further studies of otosclerosis have been done by various authors who have described pathologic features of otosclerosis. The first fundamental analysis of the pathology of otosclerosis was introduced by Nager [6] and Ogilvie and Hall [7]. In 1962 Ogilvie and Hall [8] recognized the otosclerotic lesions in a particular topographic region of the human temporal bone, the fistula ante fenestram and the cartilaginous cell nests called globuli interossei. These globuli interossei are localized within the otic capsule and are considered a 'locus minoris resistentiae'. The fistula ante fenestram is a fibrous, highly vascularized region of the temporal bone which allows communication between the mucous membranes

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of the middle ear and the enchondral layer of the otic capsule [9].

The otosclerotic focus may be localized in any part of the petrous temporal bone; however, there are sites of predilection. The most common site is the otosclerotic angle localized between the anterior part of the stapedial footplate, the processus cochleariformis and the bulge of the promontorium. The otosclerotic focus may extend to the stapes footplate leading to fixation of the footplate. In this case clinical otosclerosis occurs, which is characterized by conductive hearing loss. If the stapes footplate is not involved and no clinical signs are present the 10-fold more frequent histological otosclerosis occurs. Among these cases of histological otosclerosis some patients experience sensorineural hearing loss. There is controversy on whether the often intimate contact between the otosclerotic lesion and the inner ear space and the possibility that substances may reach the inner ear may lead to cochlear damage [9–11].

The most frequent onset of clinical otosclerosis is between the ages of 20 and 30 [12]; however, some cases beginning in early childhood or cases as late as at 60 years of age are known. Otosclerosis is more common in females. Clinical observations have suggested that pregnancy may lead to the growth of the otosclerotic focus with hearing impairment. However, no influence of estrogen and progesterone on the development of clinical otosclerosis has been observed [13]. Guild [14] observed otoslerotic lesions in 374 temporal bones, in 12.5% of women and 6.5% of men. The largest series of temporal bones analyzed to date is that of Guild [14]. In 1,161 specimens he found otosclerotic lesions in 4.39%; many specimens were from black people. Seifer et al. [15] found an otosclerotic focus in 8.3% of 601 temporal bones. The rate of stapes fixation in temporal bones is 0.99% [16]. The incidence of clinical otosclerosis in the populations of southern India is higher than in Europeans, while the populations of China, Japan and Indonesia suffer from the disease less frequently. Little information has been published on the incidence of otosclerosis in Africa [17]. The United States has approximately 15 million sufferers and otosclerosis is generally considered to be among the most common causes of acquired deafness [18]. Beales [17] calculated that approximately 2% of patients between the ages of 30 and 59 years suffer from deafness due to otosclerosis. Considering the cases of otosclerosis without encroachment of the oval window, the incidence of otosclerosis rises to 7% in Europe and 10% in the USA.

Morphologic investigations have shown the presence of an inflammatory process within the temporal bone

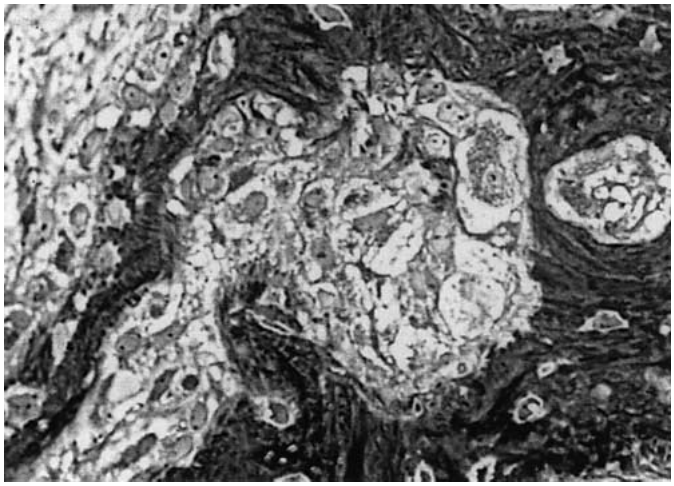

Fig. 1. Detail of an otosclerotic focus with infiltration of lamellar bone. The resorption lacuna is highly vascularized. Bouin fixation, EDTA decalcified, HE staining. × 440.

with distinct stages of bone resorption, new bone formation and final eburnization of the affected bone. Usually, the various stages coexist. In the first stage, the active, lytic or otospongiosis phase, vessels accompanied by fibroblasts penetrate into the surrounding lamellar bone (fig. 1). Because of the alteration of the chemical composition of the ground substance in sections stained with hematoxylin and eosin dark blue staining of the otosclerotic lesion is observed [19]. The inflammatory nature of this process has been clarified by immunohistochemical investigations which have revealed the presence of a variety of immunocompetent cells including macrophages, HLA-DR-positive cells, cells expressing β_2-microglobulin, T suppressor cells and complement C3 [20, 21]. Deposits of immunoglobulins (IgG, IgM and IgA) and complement C3 are present along the resorption lacunae as well in osteocytes and chondrocytes surrounding the destructive process [21, 22] (table 1). In the first stage bone resorption by osteoclasts occurs because of an unknown stimulus.

The second stage of new bone formation is characterized by a decrease of macrophages and osteoclasts while around the perivascular spaces a characteristic immature basophilic bone (blue mantels di Manasse) is reconstructed. The vascular spaces are filled with connective tissue and collagen fibrils are synthesized. The last inactive stage shows a gradually complete obliteration of the lacunae and a new dense, compact bone is formed. Characteristically, this displastic bone has a woven pattern seen in the polarized light.

Table 1. Immunohistochemistry of otosclerosis

	Otospongiosis	Otosclerosis
IgG	+++	(+)
IgA	+++	(+)
IgM	–	–
Measles virus Ab	+++	(+)
Plasma cells	++	–
T cells	+++	+
B cells	++	(+)
Complement C3	+++	++
Macrophages	+++	+
β_2-Microglobulin	+++	+

Table 2. Etiopathogenetic hypothesis of otosclerosis

Toxic substances
Mechanical stress
Vascular disturbances
Enzymatic disorder
Localized form of osteogenesis imperfecta
Localization of Paget's disease
Genetic hypothesis
Collagen (auto)immunity
Viral infection

Etiologic Hypothesis

Various hypotheses for otosclerosis have been proposed (table 2). In the past it was assumed that toxic substances play a part but because of a lack of evidence they can be disregarded. Mayer [23] and later Sercer and Krmpotic [24] assumed that because of the upright walking of humans stresses and strains may be present within the temporal bone which could lead to the formation of otosclerotic lesions. Ogilvie and Hall [8] considered otosclerosis as a localized form of osteogenesis imperfecta but not explanation for the particular predilection of the site could be given. Because of the striking histological similarity between Paget's disease and otosclerosis a localization of Paget's disease within the temporal bone has been suggested. The lack of evidence of a significant clinical association between these two conditions does not support their view. Vascular disturbances of a genetic origin were indicated by Arnold and Plester [25, 26] and Wright [27] suggested that a pathologic process of the vessels may cause necrosis with following bone resorption. Finally, an enzymatic disorder as a result of a disturbance of the trypsin-antitrypsin balance within the otosclerotic focus was suggested with a spreading of enzymes into the otic capsule [28–30].

The following three hypotheses turn out to be the most accredited ones: a genetic hypothesis, a collagen (auto)immunity and viral aetiopathogenesis.

Collagen (Auto)Immunity

Morphologic investigations have shown the origin of the otosclerotic focus within the otic capsule. In this very specific region of periostal and enchondral ossification the enchondral layer contains peculiar cartilaginous remnants, the globuli interossei, which persist throughout life. Since 1933 this feature together with certain anatomical defects such as the fistula ante fenestram has been considered to be of fundamental importance to the otosclerotic process [31]. In 1980 the concept of an autoimmune reaction from the otic capsule to the cartilaginous tissue of the globuli interossei was picked up by Carne. Further studies with experimental animals by Yoo et al. [32] supported the hypothesis of an autoimmune process as the pathomechanism of otosclerosis. The implantation of bone of the otic capsule containing globuli interossei into rats has led to the formation of otosclerotic lesions. By contrast, Harris et al. [33] reexamined this study and they could not find any otosclerotic lesion. On immunizing rats with collagen type II lesions resembling otosclerotic foci within the otic capsule were present in animals which were observed for more than 6 months after immunization [34]. Antibodies against collagen II were described by Yoo et al. [35] in the serum of patients suffering from otosclerosis and Ménière's disease. Bujia et al. [36] found serum antibodies against collagen IX significantly increased in comparison with controls, while the antibodies against collagen II were not significantly raised. By contrast to the results of Yoo et al., Sorensen et al. [37] using pepsin-purified bovine collagen type II in a well-described patient group could not confirm elevated anti-collagen II serum levels. Analyzing the patients and controls, Lolov et al. [38] found no statistically significant difference of anti-collagen type II antibodies in patients with otosclerosis and controls, but there was a significant difference in the level of antibodies in patients with the onset of the disease 3–5 years before analysis compared to other otosclerotic patients. Lolov et al. concluded that elevated serum antibodies during tissue reparation in the otosclerotic stage may be a transient response to sustained excess antigen turnover in the primary lesion.

Finally mutations of the collagen gene COL1A1 which leads to a reduction of the collagen type I synthesis have been observed in a small proportion of patients with otosclerosis [39]. This condition is similar to that which is seen in some cases of the mild form of osteogenesis imperfecta.

In summary, there are contrasting reports concerning a collagen involvement in otosclerosis. The alteration of collagen type I synthesis may be one cause in some cases of otosclerosis. Since collagen type II is widely distributed in the ear as well as in hyaline cartilages connections with other accompanying diseases of the connective tissue should by expected in otosclerosis.

Heredity

The role of heredity in otosclerosis is well established. In the middle of the 19th century Toynbee [2] suggested a familial pattern in conductive hearing loss due to the thickening of a part of the stapedial footplate. Magnus added another report of a familial case of conductive hearing loss. At the beginning of the last century Hammerschlag [40] published his work on the heredity of otosclerosis. The first who has recognized an autosomal dominant inheritance of otosclerosis was Albrecht [41] and this view has been supported by recent epidemiologic studies. Morrison [42] presented a detailed survey of 150 patients in 1967. He calculated that there must be an autosomal dominant inheritance with an about 40% penetrance. Further data coming from twins suffering both from otosclerosis gave strong evidence of a genetic etiology for otosclerosis.

In the mild osteogenesis imperfecta mutations of the collagen gene COL1A1 are well known leading to a marked reduction of the collagen type I production. Analyzing this gene with three polymorphic markers in patients with clinical otosclerosis McKenna et al. [39] found a statistically significant association between clinical otosclerosis and gene defects in the collagen gene COL1A1.

In 1998 Tomek et al. [43] presented a study of a large family with autosomal dominant inheritance of otosclerosis. In some patients clinical otosclerosis was confirmed at the site of surgery. By multipoint linkage analysis a gene for otosclerosis (OTSC1) was localized on chromosome 15q25-q26, but the gene has not yet been cloned. The most interesting gene mapped to this region is aggrecan which is an essential component in the formation of the bony labyrinth of the inner ear.

Recently a second gene for otosclerosis has been mapped in a Belgian family with autosomal dominant disease. In this family with 31 members and 18 cases, clinical otosclerosis was confirmed by surgery in 10 members. The linkage to the locus OTSC1 was excluded in all 25 members analyzed, but a linkage to chromosome 7q was found. The gene named otosclerosis 2 (OTSC2) was mapped to chromosome 7q34-36 [44].

Very recently, a third otosclerosis gene has been found named OTSC3 [pers. commun.]. The candidate regions for the published genes OTSC1 and OTSC2 are large and for the identification of the gene additional families should be studied. A familial incidence has been described in about 50% of cases suggesting an important role of heredity; however, in central Europe the familial cases of otosclerosis seem to be rare.

Measles Virus Hypothesis

Morphologic investigations have shown the presence of a chronic inflammatory process within the otosclerotic tissue with distinct stages of bone resorption, new bone formation and final eburnization of the affected bone. The inflammatory nature of this process has been clarified by immunohistochemical investigations which have revealed the presence of a variety of immunocompetent cells including macrophages, HLA-DR-positive cell, cells expressing β_2-microglobulin, T suppressor cells and complement C3 [20, 21]. Deposits of immunoglobulins (IgG, IgM and IgA) and complement C3 are present along the resorption lacunae as well as in osteocytes and chondrocytes surrounding the destructive process [21, 22]. The factor stimulating the proliferation and aggressive infiltration of the blood vessels into the bone is not known. Electron-microscopic investigations of otosclerotic tissue have revealed the presence of structures very similar to paramyxoviral nucleocapsides within osteoblasts. Analogous results have been previously obtained in Paget's disease, which histologically is very similar to otosclerosis. Immunohistochemical studies have shown the expression of measles virus nucleocapsid (N) [21] and fusion (F) [45] proteins in chondrocytes (fig. 2), in osteocytes, in osteoblasts and in the connective tissue, especially in otospongiotic (resorptive) areas. The presence of measles virus RNA within tissue from patients with clinical otosclerosis has been detected by RT-PCR [46] and these results were confirmed by McKenna et al. [47]. They analyzed celloidin-embedded temporal bone specimens with the histological evidence of the presence of otosclerotic tissue. By contrast, Bozorg Grayeli et al. [48] analyzing 30 cases with RT-PCR did not find measles virus-related sequences. However, the extraction of control genomic RNA (GAPDH) was successful in only 22 of 30 cases. Since the otosclerotic focus is in the case of clinical otosclerosis in

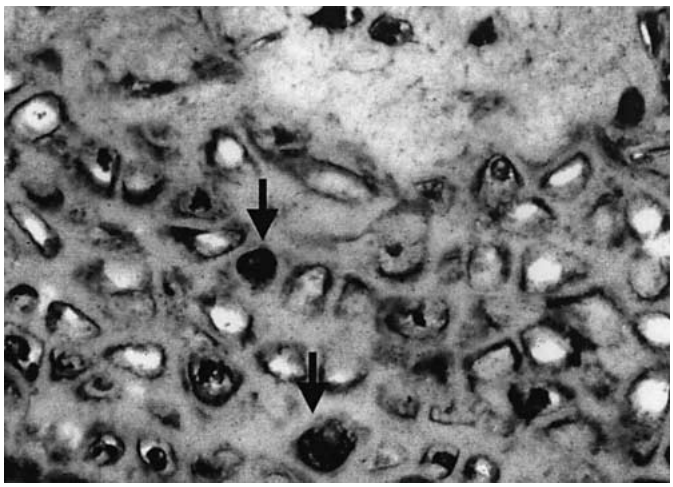

Fig. 2. Immunohistochemical detection of measles virus antigens in otospongiotic tissue. Chondrocytes (arrows) express measles virus N protein. Bouin fixation, EDTA decalcification, ABC. × 432.

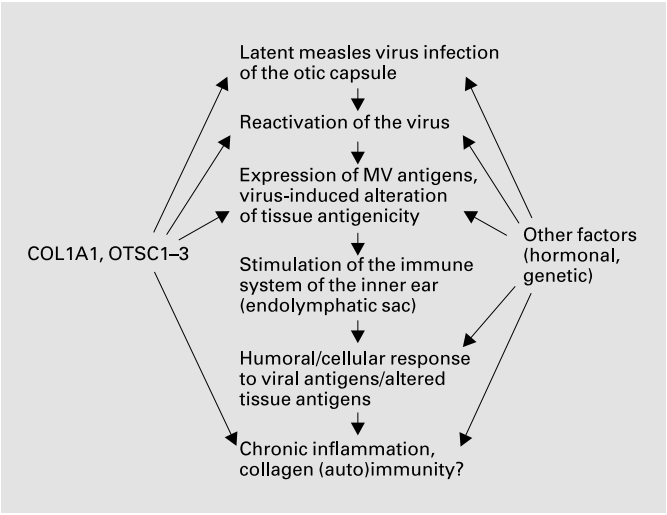

Fig. 3. Hypothesis of a pathway in otosclerosis. MV = Measles virus.

intimate contact with inner ear spaces an antibody reaction against measles virus proteins could be expected. In fact, analyzing the perilymph of patients suffering from clinical otosclerosis, the amount of specific measles virus IgG in comparison with total IgG is higher within the perilymph than within the serum [49].

Finally, epidemiologic data support a measles virus involvement in the etiopathogenesis of otosclerosis [50]. Before the introduction of the measles vaccine the age of onset of hearing loss due to an otosclerotic fixation of the stapes was found to be between the age of 15 and 40 years with a 1.4 higher incidence in women. If the measles virus plays a certain role in the etiopathogenesis of otosclerosis, measles virus vaccination should reduce the incidence of otosclerosis in the younger population. The univariate and the multivariate analysis of 1,351 patients with clinical otosclerosis and subjected to stapes surgery between 1978 and 1999 showed a statistically significant increase of the patient age over the period examined. The decrease in the incidence of otosclerosis in younger people is simultaneous with the widespread administration of measles virus vaccination in Germany.

Conclusion

Otosclerosis is a chronic inflammatory disease exclusively of the human temporal bone. The disease has a high incidence and is considered the be among the most commen causes for acquired deafness. The major etiopathogenetic hypotheses of otosclerosis considered are genetic factors, collagen defects and collagen (auto)immunity and viral infection. There is controversy as regards all these hypotheses and it seems likely that different factors contribute to the genesis of otosclerosis (fig. 3).

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