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REVIEW ARTICLE

An overview of the etiology of otosclerosis

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Abstract Otosclerosis is the primary disease affecting the homeostasis of otic capsule and is among the most common causes of acquired hearing loss. Otosclerosis is considered as a multifactor disease, caused by both genetic and environmental factors. The aim of the present review is to summarize and analyze the bibliographic data, associated with the etiology of the disease. In some cases, the otosclerosis has an autosomal dominant mode of inheritance with incomplete penetrance. Genetic studies reveal the occurrence of at least nine chromosomal loci as candidate genes of the disease. The localized measles virus infection of the otic capsule has been postulated as a possible etiological theory. The role of hormonal factors, immune and bone-remodeling system in the etiopathogenesis of otosclerosis and the association of the disease with the disorders of the connective tissue are the issues of the present study. Despite the extensive research, many etiological factors and theories have been suggested and the process of development of the otosclerosis remains unclear.

Keywords Otosclerosis · Otospongiosis · Etiology · Pathogenesis · Genes · Inheritance · Measles virus · Review

Introduction

Otosclerosis is the term used to describe the primary disease of the otic capsule that is characterized by alternating phases of absorption of compact bony tissue and replacement with spongy bone. The above description of the disease explains the use of the term ‘otospongiosis’, which is more accurate from the pathological point of view, from a considerable number of researchers. The emergent bony tissue is characterized by higher density, cellularity and vascularity and the most common site of location is the oval window that causes the stapedial ankylosis.

The Italian anatomist and surgeon Antonio Maria Valsalva, in 1741, first reported a lesion of otosclerosis that appeared in a dissection of the temporal bone from a patient who was believed to had been deaf [1]. Valsalva remarked that the footplate of the stapes had become ankylosed by ossification of the annular ligament. The term “otosclerosis” was coined by von Troltsch in 1869, referring to the final inactive stage of the process and was introduced by Politzer, in 1894, who described the otosclerotic temporal bone of the final stage of disease [2, 3]. Siebenmann, in 1912, proposed the term “otospongiosis” to designate the active stage of the disease, a term still used in Europe and mainly by our French colleagues [4]. In 1873, Schwartze first described the reddish blush on tympanic membrane, which is established as Schwartze sign and is significant of active disease due to the prominent vascularity associated with the otospongiotic focus.

Otosclerosis is the cause of 5–9% of the cases with hearing loss and of 18–22% of conductive hearing loss [5, 6]. The disease is bilateral in 70–80% of patients and the symptoms occur depending on the site of the otosclerotic focus [7]. Hearing loss, vertigo and tinnitus are the main features of the symptomatology of the clinical form of the disease, which should be distinguished from the histological. Histological otosclerosis is the term for the description of the abnormal bone capsule on microscopic view without clinical signs.

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The prevalence of the clinical otosclerosis has a considerable racial variation and ranges from 0.04 to 1% in Caucasian people [8–13]. On the contrary, in Asian countries the incidences of clinical otosclerosis is much lower and approximately zero in blacks, with a few exceptions in natives globally [14–16]. The prevalence of histological otosclerosis is about ten times higher than clinical and reaches the rate of 10% in Caucasians. Epidemiological studies reveal that the prevalence of histological otosclerosis in Asians and blacks is 5 and 1%, respectively [17, 18].

A considerable number of bibliographic reports have noted a female to male ratio of clinical otosclerosis of 2:1 [19–21]. Histological studies do not confirm the sex ratio difference [8, 17, 21]. The age of onset of clinical otosclerosis ranges between 16 and 30 years [9, 19, 22, 23].

The true nature and the mechanism of pathogenesis of otosclerosis remain not clearly understood despite the intensive research and the great body of literature that has been published. The aim of the present review is to try to summarize the whole series of theories that have been postulated regarding the etiology of otosclerosis.

Genetic factors

The higher incidence of otosclerosis in certain families, comparing with the general population, clarifies the genetic background of the disease.

Type of inheritance

Several types of inheritance have been suggested. Nowadays, the autosomal dominant character of inheritance with incomplete penetrance and variable expressivity is considered as the most possible, according to a great body of literature. The term incomplete penetrance refers to the phenomena where a portion of individuals with a disease-associated genotype do not develop the disease. Variable expressivity occurs when all develop the disease in some manner but to varying degrees.

In 1922, Albrecht [24] was the first to indicate the autosomal dominant inheritance while, in 1925, Bauer and Stein [25] proposed the autosomal recessive character, after the study of 94 families with otosclerosis. The rate of penetrance is estimated to be 40%, based on several epidemiological studies. Firstly, Larsson et al. [22], reviewing all cases with otosclerosis seen in the University of Goteborg Hospital from 1949 to 1957, concluded that autosomal dominant inheritance with penetrance between 25 and 40% accounted for his findings. In 1967, Morrison [9] presented a survey of 150 English cases and their families and he proposed that otosclerosis inherits by a dominant character with less than 50% penetrance. Furthermore, Causse et al. [11] supported the autosomal dominant with 40% of penetrance, studying 614 families with 1,465 cases affected with clinical otosclerosis.

"Sporadic" cases

The majority of the bibliographic reports underline that only a rate of 50–70% of cases with otosclerosis have positive family history and the rest are considered as "sporadic" cases (patients without family history) [9, 10, 22].

Morrison and Bundey [26] cited the following reasons as possible explanations of the occurrence of sporadic cases: (1) phenocopies (the false positive cases), (2) the new mutations, (3)the failure of expressivity and (4) the autosomal recessive inheritance. The last explanation was considered as the most probable as it justified the rates of histological and clinical otosclerosis, which were 7 and 0.3%, respectively. The same authors assumed that histological otosclerosis is demonstrated in heterozygous recessive cases and in patients with positive family history and incomplete penetrance. Contrary to above conclusions, Ben Arab et al. [27] reported, after a study of 193 families in North Tunisia, that only 13% of the cases had positive family history and the type of inheritance was the autosomal dominant with complete penetrance.

The insufficient explanation of the type of inheritance by autosomal dominant character in all cases of otosclerosis had as consequence the seeking of alternative modes of transmission. In 1978, Schaap et al. speculated the coexistence of autosomal dominant and X-linked inheritance with the natural selection to be against the males [28]. Furthermore, the X-linked dominant or recessive inheritance was not supported from the results of other studies and the prevalence of the disease in the two genders [10, 22].

Relation with different genetic factors

Concurrently with the seeking of alternative modes of transmission of otosclerosis, there was an attempt to relate the etiology of the disease with certain genetic factors. Chromosomal abnormalities, such as trisomy and tetrasomy mosaics of chromosomes 13 and 15 were reported by Tato et al. [29], without these assumptions to be confirmed by the analysis of the karyotype of patients with otosclerosis. Jannuzzis et al. [30] proposed an association between otosclerosis and ABO groups, suggesting the possible close location of the genes of the two diseases. However, this view had never been confirmed and years later Morrison disputed the validity of this study [26]. Other studies tried to isolate the otosclerosis gene by examining the relation with a known gene complex or particular clinical feature such as iris color or hair color [30], without their results to be certified [9, 26].

Browsing the gene of otosclerosis

To date, the research interest has been focused on screening the human genome and isolating certain chromosomal loci and genes that are associated with the otosclerosis (Table 1).

The first effort was carried by McKenna et al. [31], by conducting an association study using polymorphic DNA markers from patients with clinical otosclerosis (with or without family history) and random control subjects. This study showed a significant association between clinical otosclerosis and the type I collagen COL1A1 gene (17q21.31–q21.32) using three different polymorphic markers within it. The role of COL1A1 gene is the production of type I collagen and the mutations of this gene causes the mild modes of osteogenesis imperfecta. The above researches concluded that some cases of clinical otosclerosis may be related to mutations within the COL1A1 gene that are similar to those found in mild forms of osteogenesis imperfecta and result in null expression of the mutant allele. Same authors, in 2004, reported an association between otosclerosis and osteoporosis, as may share a functionally significant polymorphism in the Sp1 transcription factor binding site in the first intron of the COL1A1 gene [32]. The possible association between otosclerosis and COL1A1 gene polymorphisms was not confirmed by a case-control sample from a population of Caucasian individuals living in Northwest Spain [33].

In 1998, Tomek et al. [34] isolated a chromosomal locus, OTSC1 (15q25–q26, after a study in a large multi-generational family, from South India, in which otosclerosis has been inherited in an autosomal dominant pattern. In order to locate the disease-causing gene they completed genetic linkage analysis using short tandem repeat polymorphisms (STRPs) distributed over the entire genome. A gene that has been mapped to the 15q25–q26 interval produces the aggrecan, the quantitatively major non-collagenous component of the extracellular matrix of cartilage [35]. This gene is an excellent candidate for a major role in the pathogenesis of otosclerosis for four reasons: (1) aggrecan is a complicated protein for which there are several different alleles; (2) the bony labyrinth of the inner ear develops from a cartilaginous precursor in which aggrecan is expressed; (3) mutations in the homologous mouse mutant produce hearing impairment; and (4) glycosaminoglycan side chains bind to aggrecan and can be utilized by microorganisms for binding to target cells.

The second possible gene of otosclerosis, the OTSC2, was reported by Van Den Bogaert et al. in 2001. In this study, the researches performed a linkage analysis in a Belgian family in which otosclerosis inherits as an autosomal dominant disease. Firstly they excluded the linkage to the known locus on chromosome 15 (OTSC1) and then they identified linkage on chromosome 7q. Further analysis mapped this otosclerosis locus (OTSC2) to a 16-cM interval on chromosome 7q34–36 [36]. Recently, Alzoubi et al. [37] proposed the exclusion of the linkage between otosclerosis and the locus of OTSC2. The same authors suggested the low power of the available studies regarding the etiology of the disease, indicating the need of non-parametric linkage analysis on large numbers of extended pedigrees.

After a year, Chen et al. identified a third chromosomal locus, the OTSC3 (6p21.3–22.3), studding a large Cypriot family segregating otosclerosis and excluding linkage to OTSC1 and OTSC2. The defined OTSC3 interval covers the human leukocyte antigen (HLA) region, consistent with the reported associations between HLA-A/HLA-B antigens and otosclerosis (analysis in section below) [38].

The fourth chromosomal locus that has been associated with otosclerosis, the OTSC4 (16q22.1–23.1), owes its existence to the study of Brownstein et al. [39] in Israeli family. The OTSC4 interval includes several genes involved in the immune system and bone homeostasis that may be the good candidates for the genes of otosclerosis.

The identification of another chromosomal region, the 3q22–24, considered as the fifth possible locus of otosclerosis

Table 1 Summary of the chromosomal loci associated with otosclerosis

Study	Year	Country of the family	Chromosomal locus	
McKenna et al. [31]	1998	USA	COL1A1	17q21.31–q21.32
Tomek et al. [34]	1998	India	OTSC1	15q25–q26
Van Den Bogaert et al. [36]	2001	Belgium	OTSC2	7q34–q36
Chen et al. [38]	2002	Cyprus	OTSC3	6p21.3–22.3
Brownstein et al. [39]	2006	Israel	OTSC4	16q22.1–23.1
Van Den Bogaert et al. [40]	2004	Denmark	OTSC5	3q22–24
a	a	a	OTSC6	a
Thys et al. [42]	2007	Greece	OTSC7	6q13–16.1
Ali et al. [43]	2007	Tunisia	OTSC8	9p13.1–9q21

[a] Reported to the Human Genome Organisation nomenclature committee but details describing this locus have not been published

(OTSC5), despite the fact that it antedates OTSC4. It derives from the studies of Van Den Bogaert et al. in a Danish family [40]. In addition, a sixth locus, OTSC6, has been reported to the Human Genome Organisation nomenclature committee but details describing this locus have not been published yet.

In 2006, Iliadou et al. [41] performed a linkage analysis in a family with 16 cases in Greece and excluded linkage to the known otosclerosis loci (OTSC1, OTSC2, OTSC3, and OTSC5) and to COL1A1 and COL1A2. A year later, the same authors reported the identification of the seventh locus, OTSC7 that was localized on chromosome 6q13–16.1 [42]. Furthermore, the above researchers performed linkage analysis of this new locus in 13 smaller Belgian and Dutch families, locating one family from Netherlands in which allele isolation seems to be associated to this seventh region.

Finally, an eighth chromosomal locus has recently been reported by Bel Hadj Ali et al., who presented the results of a genome-wide linkage analysis in a large Tunisian family segregating autosomal dominant otosclerosis. Linkage analysis localized the responsible gene to chromosome 9p13.1–9q21.11 and this locus was named OTSC8 [43].

Virus etiology

The first attempts

Firstly, McKenna et al. [44], in 1986, postulated the theory of virus etiology for the otosclerosis, observing filamentous structures morphologically similar to viral nucleocapsids in osteoblast-like cells of otosclerotic lesions in two patients. A year later, the theory of virus etiology of otosclerosis was supported by the findings of Arnold et al., who observed high concentration of antibodies of the IgG-class in active otosclerotic lesions and less pronounced in the cytoplasm of the cells of the adjacent enchondral layer. Furthermore, the above authors, using polyclonal antibodies against measles and rubella viruses, noticed that both the antigens were expressed both by the chondrocytes of the enchondral layer and occasional osteocytes and osteoclasts of the otosclerotic lesion. In the same study, IgG antibodies or viral antigens were absent in the normal bone of the stapes specimens [45].

Antibodies IgG, IgA, IgM against mumps, measles and rubella antigens were also found in a study of Arnold et al., in 1988, showing the expression of the relevant viral antigens in the large cells of the resorption lacunae, in the vascular connective tissue, and in osteocytes, osteoclasts and chondrocytes, present in or around the otospongiotic areas of 42 patients. In the same study, healthy footplates showed neither a deposition of antibodies nor any expression of viral antigens. According to the above results, authors favoured the viral etiology of otosclerosis as an inflammatory vascular reaction of the otic capsule initiated or caused by the viruses of measles, rubella and mumps [46]. In an another study, Arnold et al. [47] suggested that the absorption of natural compact bony tissue and the replacement with spongy bone are stages of an inflammatory procedure, as 80% of the lymphocytes present in the otosclerotic footplate were revealed to be T-lymphocytes.

Despite the above reports, the theory of virus etiology remains unsettled and controversial. The objectors of virus theory support that the measles virus exists in normal human tissues and the studies that support virus etiology derive from USA, where the vaccination against measles started at the beginnings of 1960 [48]. In 1992, Roald et al. [49] reported the findings of his study, which are in accordance with the above limitations of virus theory. According to this report, a series of viral antigens, including adenovirus, influenza A and B, parainfluenza types 1 and 3, measles, mumps, respiratory syncytial and Epstein Barr viruses, were not isolated in a prospective series of stapes specimens collected from 24 consecutive patients operated on for otosclerosis. With the exception of one case of positive specific reactivity for anti-RSV antibody in one multinuclear osteoclastic cell, no specific reactivity was seen in the specimens.

Molecular analysis

The introduction of the molecular analysis has increased the diagnostic tools, adding new reports regarding the association between etiology of otosclerosis and viruses.

In 1994, Niedermeyer et al. [50], being benefited from the capabilities of reverse transcriptase polymerase chain reaction (RT-PCR), detected measles virus-related sequences in footplate fragments from approximately half of the patients with clinical otosclerosis. Actually, this study supported, at the molecular level, the results previously found by immunohistochemistry. In the same year, McKenna and Kristiansen [51] successfully demonstrated measles virus genome in fixed and decalcified tissue sections of temporal bones from patients with otosclerosis.

In 1995, Niedermeyer et al. supported the previously stated hypothesis that otosclerosis is a measles virus associated disease which provokes a local immune response within the inner ear. The authors not only detected measles virus RNA sequences in patients with otosclerosis, but also IgG anti-measles virus antibodies in the perilymph 6 of 13 patients.

In 2000, Niedermeyer et al. [50, 52, 53] in a study of 95 patients with otosclerosis, examining footplate fragments using RT-PCR, evidenced the existence of same measles virus nucleocapsid mRNA as in previous reports of the

same authors. Quantification of measles virus IgG in the perilymph and serum of otosclerosis patients confirmed the previous result that the ratio of antimeasles virus IgG to total IgG was higher in the perilymph than the serum. Furthermore, the authors stated that, since the initiation of a measles vaccination program in Germany, there had been a decline in the incidence of otosclerosis, and the average age of patients at diagnosis and surgery at their hospital had increased to 54 years. Consistent to the above state, Arnold et al. [54], correlating the measles vaccination programme in Germany with the incidence of otosclerosis in the same country in the period of 1993–2004, suggested a causal association between measles virus infection and otosclerosis.

The above limitations of the virus theory determined Shea [55] to state: "*If the measles virus is the cause of the growth of the otosclerotic focus, as it seems to be, then vaccination against measles eventually will eliminate the hearing loss of otosclerosis completely*". In 2000, Grayeli et al. [56] tried to investigate the presence of the measles virus in pathologic stapes samples from 35 patients by different sensitive methods. The authors did not supported the evidence of the presence of the measles virus in any of the bone samples or primary bone cell cultures.

Recent data

Recent data in global literature support the hypothesis of involvement of measles virus in the etiology of the otosclerosis. The main studies of the last 5 years, supporting the virus theory, are presented in Table 2.

Karosi et al., in a series of studies that have published from 2004 to 2007, confirm the detection of measles virus genome in a considerable rate of otosclerotic stapes. Moreover, they identified the existence of inflammatory agents, such as the glycoprotein CD51/61 and CD46 and cytokine TNF-α, and the activity of osteoprotegerin and alcalic phosphatase, demonstrating activated osteoclast functions and inflammatory pathways in otosclerotic stapes footplates associated with measles virus presence [57–63, 65, 66]. The same authors argued that non-otosclerotic stapes fixations could be established as pseudo-otosclerosis and may belong to non-specific, degenerative disorders and otosclerosis is an inflammatory disease caused by persisting measles virus infection of the otic capsule [57].

In 2007, Niedermeyer et al., performing RT-PCR, localized measles virus sequences in osteoclasts, osteoblasts, chondrocytes, macrophages, and epithelial cells in middle ear mucosa of otosclerotic tissues. Genotyping of measles virus in otosclerotic foci demonstrated the presence of virus with genotype A, which circulated in Europe around 1960, confirming further the strong association between measles virus infection and otosclerosis [67].

In the same year, Lolov et al. suggested that otosclerosis should be considered as an organ-specific measles virus-induced disease, as the results of his study are consistent with viral participation in otosclerotic pathogenesis. The same authors clarified that it is difficult to state if the diminished antimeasles humoral response is a consequence of or the cause for a local measles infection [68].

Endocrine factors

Otosclerosis and pregnancy

Endocrine factors have been involved in the etiopathogenesis of the otosclerosis, due to the fact that the disease' symptoms are often manifested during or shortly after pregnancy.

Since 1930, many researchers have reported the occurrence or the aggravation of the hearing loss in 30–60% of women with otosclerosis, who had at least one pregnancy (Table 3). In 1951, Pearson [72], documenting the coincidence of otosclerosis and pregnancy, proposed the termination of pregnancy and sterilization as treatment in progressive cases. However, the real origin for the above argument seems to have begun with a paper by Greifenstein, which outlined guidelines from the German Reichsgutacherstelle (Agency of Expert Opinion of the German Reich) about abortion and sterilization for the eugenic reason of terminating a genetic disease [73]. This guideline had as conclusion, in 1939, of 69 women with otosclerosis in Germany, 43 had an abortion and 23 were sterilized.

Otosclerosis is more common in women, more likely to occur during childbearing ages and the question that reveals is if the hormonal changes during pregnancy are the trigger to the manifestation of the disease or pregnancy is just an incidental event. Therefore, hormonal influence of oral contraceptives does not appear to predispose the female population to an increase in otosclerosis. Despite the established participation of estrogens in osteoblastic function, their role to the pathogenesis of otosclerosis remains unsettled. The review of the literature indicates that the reports of occurrence or aggravation of otosclerosis during pregnancy (Table 3), omit to report data regarding the age of onset in women, the number of their pregnancies and the level of their hearing loss. The above remarks dispute the role of the hormonal background during pregnancy in the pathogenesis of otosclerosis.

The first objections to the role of pregnancy to the clinical course of otosclerosis were made by Hall et al. [74], in 1974, who reported that only 107 (8%) of 1,341 women with otosclerosis had aggravation of their disease during pregnancy. Recent data found no adverse effect on hearing in otosclerotic women who had children compared with

Table 2 Recent data supporting the virus theory

Study and year	Method	Result
Karosi et al. 2005 [58]	Amplification of Me-V nucleoprotein RNA by RT-PCR	Me-V RNA was contained in 99 of 154 (64%) stapes footplate specimens
	Detection of TNF-α mRNA expression by RT-PCR	TNF-α mRNA was detectable in 88 virus-positive and in 6 virus negative stapes footplates
Karosi et al. 2006 [62]	Detection of coexpression of TNF-α and osteoprotegerin mRNA by RT-PCR and correlation to measles virus positivity	Osteoprotegerin mRNA expression was significantly lower in the TNF-α- positive specimens ($P < 0.0001$), independently from virus positivity
Karosi et al. 2006 [63]	Amplification of Me-V nucleoprotein RNA by RT-PCR	Me-V RNA was contained in 175 of 271 (65%) stapes footplate specimens
	Correlation of amplification results to postoperative histologic and CD51/61 specific immunohistologic findings	Osteoclasts of otosclerotic foci showed positivity for CD51/61 antigen Expression level of CD51/61 complex was strongly associated with the histologic grade of otosclerosis ($P < 0.005$)
	Assessment of alcalic phosphatase activity	Alcalic phosphatase activity was significantly higher in otosclerotic foci compared with nonotosclerotic stapes ankylosis ($P < 0.001$)
Gantumur et al. 2006 [64]	Amplification of Me-V nucleoprotein RNA by RT-PCR to four fresh frozen footplate bone fragments	None of the four samples yielded the expected RT-PCR products
	Amplification of Me-V nucleoprotein RNA by RT-PCR to cells of 16 primary cultures of otosclerotic tissue samples	MeV-specific PCR products were detectable in 5 of the 16 (30%) samples
Karosi et al. 2007 [66]	Amplification of Me-V nucleoprotein RNA by RT-PCR	Me-V RNA was contained in 87 of 116 (75%) stapes footplate specimens
	Correlation of amplification results to postoperative histologic and CD46 specific immunohistologic findings	In active otosclerosis, increased numbers of osteoclasts showing strong CD46 expression. In virus negative, non-otosclerotic stapes fixation and in normal stapes footplates weak CD46 immunoreaction on the osteocytes and fibroblasts
Niedermeyer et al. 2007 [67]	Amplification of Me-V nucleoprotein RNA by RT-PCR	Localization of Me-V, genotype A, sequences in osteoclasts, osteoblasts, chondrocytes, macrophages, and epithelial cells in middle ear mucosa of otosclerotic tissue
	Detection of anti-Me-V in perilymph and serum	Elevated anti-Me-V IgG levels were detected in the perilymph of patients with otosclerosis in comparison with the serum levels

Me-V measles virus, *TNF-α* tumor necrosis factor-alpha

Table 3 Occurrence or progression of otosclerosis's symptomatology in women due to at least one pregnancy

Study	Sample size	Rate of occurrence or progression of symptoms (%)
Schmidt et al. 1933 [69]	49	51
Cawthorne et al. 1955 [70]	419	63
Larsson et al. 1960 [22]	104	46
Morrison et al. 1967 [9]	63	55
Gapany-Gapanavicius et al. 1975 [10]	338	21
Gristwood et al. 1983 [71]	479	33–63

women without children [75]. Furthermore, air conduction, bone conduction, and discrimination were not worse in women with children versus childless women. The same study reported no significant correlation between the number of children and hearing loss, and neither did breastfeeding affect the amount of hearing loss.

Parathyroid function

The theory that otosclerosis is a general skeletal bone disease and the abnormal parathyroid function contributes to its progress has been first postulated by Wright et al., in 1974. However, Jensen et al. supported the assumption that otosclerosis is a localized disease of otic capsule and not a manifestation of a generalized disorder of the skeletal system, measuring the mineral content of skeletal bone and the serum levels of calcium and phosphorus in case-control study [76]. Moreover, Lolov et al. [77] observed that patients with otosclerosis had significant high concentration of alkaline phosphatase only when the disease had duration between 3 and 5 years compared with other patients. Finally, Grayeli et al. [78] supported the hypothesis that an abnormal cellular response to parathyroid hormone (PTH) contributes to the abnormal bone turnover in otosclerosis, giving a new dimension to the etiology of the disease.

Immune system

Autoimmunity has been suggested as a possible causative factor of otosclerosis, but the reported data remain contradictory.

Auto-antibodies

The theory of auto-antibodies first postulated by Yoo et al. [79], who reported elevated levels of antibodies to type II collagen in sera, otic foci and perilymph of patients with otosclerosis. The same theory supported that the disease is caused by autoimmune response to embryonic cartilaginous remnants of otic capsule. The above theory is in agreement with the findings of other researchers, who confirmed the immune involvement in the etiology of the otosclerosis, especially in patients with the disease of long duration [77, 80]. In contrast to the above hypothesis, Sorensen et al. [81] found no difference in otosclerotic patients compared with controls in levels of type II collagen. Furthermore, in animal models, the results regarding the role of immunity in leading to otosclerosis-like bone lesions in the otic capsule are conflicting [82, 83].

HLA and otosclerosis

The evidence for the association of otosclerosis with the HLA system is controversial. Menger et al. [84] published an extensive review about the studies that report the role of immune system and especially HLA in the etiology of otosclerosis. According to a considerable body of literature, there is an association between specific HLA antigens and otosclerosis [85–87]. However, the findings of other studies are not in agreement with the above conclusions [88, 89].

Bone remodeling

Bone remodeling is a continuous natural process that is ongoing throughout the skeleton, with the exception of otic capsule. Under normal circumstances, bone absorption by osteoclasts is followed by an equal bone formation by osteoblasts.

Fundamental parameters of the process of bone remodeling are the members of the transforming growth factor-b (TGF-b) superfamily that includes the prototype of the family, the TGF-bs, the bone morphogenetic proteins (BMPs) and activins. Moreover, TGF-b1, another member of TGF-b superfamily, contributes to the embryonic development of the ear. In 2007, Thys et al. [90] associated otosclerosis with TGF-b1, supporting the influence of the variants of this agent to the susceptibility of the disease. According to recent studies, specific BMPs and the polymorphisms of their genes appear to be involved in the pathologic metabolism of bone remodeling, supporting the results from the reported association of TGFB1 with the otosclerosis [91, 92].

Considering the bone remodeling at a local level, we note that the normal process depends on the balance between three cytokines: osteoprotegerin (OPG), receptor activator of nuclear factor kB (RANK), and RANK ligand (RANKL) [93, 94]. Osteoporosis is characterized by lack of OPG while overexpression of OPG causes excessive bone formation or osteopetrosis [95, 96].

As it was reported in "Virus etiology", Karosi et al. [62] detected, using RT-PCR, the coexpression of TNF-α and osteoprotegerin mRNA that demonstrates an activated osteoclast functions and inflammatory pathways in otosclerotic stapes footplates associated with measles virus presence. The same authors concluded that the increased expression of TNF-α and its action on RANK production inhibit the protective functions of osteoprotegerin on normal bone turnover in the otic capsule, supporting the role of the bone-remodeling system in the etiopathogenesis of the disease.

A recent study showed that the normal otic capsule contains very high levels of OPG (by factors of 20 or more than other bones), and that OPG is produced in extremely high concentration within the inner ear, primarily by type I fibrocytes of the spiral ligament, and secreted into the perilymph [97]. Some of this inner ear OPG may contribute to the inhibition of otic capsule remodeling by diffusing into the surrounding otic capsule bone via an intricate canalicular system. By this means, the cochlear soft tissue may control the nature of the surrounding petrous bone.

Disorder of connective tissue

Otosclerosis and disorders of the connective tissue

The hypothesis that otosclerosis is a part of general connective tissue disorder has been postulated since the first efforts seeking the etiology of the disease. The above hypothesis was based on specific similarities between otosclerosis and disorders of connective tissue, such as reduction of dermal thickness or morphologic changes in extra- or intracellular spaces of tissues [98, 99]. Nevertheless, the afterwards studies did not confirm these findings [100].

Otosclerosis and osteogenesis imperfecta

A second approach to classify otosclerosis as a disorder of the connective tissue was stated by researchers due to clinical and histopathological similarities of the disease with the osteogenesis imperfecta, such as the autosomal dominant type of inheritance and the coexistence of phases of osteoclastic and osteoblastic activity [101, 102]. Similarities like the above prompted the hypothesis that otosclerosis is a local manifestation of osteogenesis imperfecta.

Osteogenesis imperfecta is characterized by abnormal type I collagen, which is associated with mutations of COL1A1 and COL1A2 genes. In 1998, McKenna et al. [31], analyzing the COL1A1 and COL1A2 genes and their mutations, clarified the significant association of three polymorphic markers within COL1A1 gene and the otosclerosis, suggesting a potential relationship between the disease and the mild forms of osteogenesis imperfecta (type I). The above study established COL1A1 as the first possible gene in the etiology of otosclerosis, as it was analyzed in the Genetic Factors section. In 2002, the same authors, examining the further relation between the two diseases, stated that mutations in COL1A1 that are similar to those that occur in type I osteogenesis imperfecta may account for a small percentage of cases of otosclerosis, and that the majority of cases of clinical otosclerosis are related to other genetic abnormalities that have yet to be identified [103]. Consistent to the above correlation between otosclerosis and COL1A1, Chen et al. [104], in 2007, proposed a causal relationship between specific haplotypes in collagen type 1 genes and the development of the disease.

Conclusions

Despite extensive research, the literature review reveals a considerable number of theories regarding the etiology of otosclerosis, although none of them can be accepted thoroughly. The pathogenesis of the disease remains unknown. Generally, it is considered as a complex disease caused by both genetic and environmental factors.

Certainly, a genetic factor plays a significant role in the manifestation of otosclerosis, although the precise mode of inheritance is still uncertain. The autosomal dominant type of inheritance with incomplete penetrance remains the most acceptable theory. The decryption of the human genome with the assistance of the new genetic research techniques has revealed the existence of nine possible chromosomal loci (COL1A1, OTSC1, OTSC2, OTSC3, OTSC4, OTSC5, OTSC6, OTSC7 and OTSC8) that are associated with the etiology of the otosclerosis. The heterogeneity of the genetic linkage studies in association with the large size of the specific loci confuses the effort of seeking the gene of otosclerosis. Moreover, families large enough for a genetic linkage study are rare, and in these families, factors like reduced penetrance and phenocopies complicate linkage analysis.

The local measles virus infection of otic capsule has been suggested as a possible etiology theory of pathogenesis of disease. The isolation of the genome sequence of the measles virus from otosclerotic lesions has confirmed the association of the virus infection with the pathogenesis of disease. However, the epidemiological data seem to suggest

a secondary role of the particular viral infection in the pathogenesis of the disease. The theory of endocrine factors was based on the findings of occurrence or aggravation of the disease in pregnant women, without being able to detect a causative hormone. The similarities of otosclerosis with osteogenesis imperfecta revealed the possible similar underlying etiology of these diseases. The detection of the COL1A1 gene in cases of type I osteogenesis imperfecta and in patients with otosclerosis suggests an association, without the exact similarity between the two diseases can be defined.

Clearly, the etiology of otosclerosis and the mechanism of remodeling of the otic capsule remain unsettled, a fact that gives an occasion for further research efforts in order to understand thoroughly the etiopathogenesis of the disease.

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