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Review

The pathophysiology of otosclerosis: Review of current research

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ABSTRACT

Otosclerosis is a complex disease of the human otic capsule with highest incidence in adult Caucasians. So far, many possible etiological factors like genetics, HLA, autoimmunity, viruses, inflammation, and hormones have been investigated but still the development of the disease remains unclear. Currently, the surgical replacement of stapes (stapedotomy) remains the best possible treatment option. In this review, we analyze different etiological factors studied so far in otosclerosis pathophysiology and discuss most recent findings and possible new research pathways.

Contents

Abbreviations: HLA, Human Leukocyte Antigen; TGF-β, Transgrowing Growth Factor-β; BMP2/4, Bone Morphogenetic Proteins 2 and 4; SNP, Single Nucleotide Polymorphism; CD46/ CD150, Signaling lymphocytic activation molecules; IL1/6, Interleukin 1 and 6; TNF-α, Tumor Necrosis Factor-α; PTH, Parathyroid Hormone; C3a/C3b/C5a, Complement fragments 3a, 3b and 5a; RASS, Renin Angiotensin Aldosterone System; AGTM235 and ACE I/D, Genetic polymorphisms of Renin Angiotensin Aldosterone System; ROS, Reactive Oxygen Species; HNE, 4-hydoxynonenal

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1. Otosclerosis: definitions and epidemiology

Otosclerosis (localized bone dysplasia) is a primary disease of the human otic (labyrinthine) capsule and stapes footplate. Depending on the site, size, and histologic features of the pathologic involved area hearing and balance are affected. When describing otosclerosis, it is important to distinguish between the histological and the clinical form of the disease (Declau et al., 2007). Clinical/radiological otosclerosis refers to the presence of otosclerotic foci at the site where it causes conductive hearing loss by interfering with the motion of the stapes or of the round window membrane (Guild, 1944; Shambaugh, 1994; Arnold and Friedmann, 1987). Otosclerotic plaques are mainly localized anterior to the oval window (fissula ante fenestram region), and on the stapes footplate (80%), at the round window (30%), pericochlear region (21%) and the anterior part of the internal auditory canal (19%), Arnold, 2007. Other localizations although very rare have also been described: malleus, incus, facial canal, semicircular canals and endolymphatic duct (Guild, 1944). Histological otosclerosis refers to a disease process without clinical symptoms, discovered only on routine sectioning of the temporal bone. There are three forms of histologic lesions of otosclerosis: otospongiosis (early phase), transitional phase and otosclerosis (final phase). The early, active phase lesions consist of the presence of histiocytes, osteoblasts, and the most active cell group osteocytes (Fraysse et al., 1994). They absorb the bone around pre-existing blood vessels that causes higher and better microcirculation. As osteoblast becomes more involved, these areas grow rich in amorphous ground substance and deficient in mature collagen, resulting in formation of new spongy bone. With hematoxylin and eosin staining, this new bone appears densely blue known as mantles of Manasse (1912). The late phase is characterized with the formation of sclerotic, dense bone in areas of the previous bony resorption. The vascular spaces, previously dilated, are narrowed due to bony deposits. Otosclerosis begins in endochondral bone, as the spongious and sclerosis continue the endosteal and periosteal layers also become involved (Roland and Samy, 2006).

The clinical presentation of otosclerosis is mainly a conductive hearing loss, although sensorineural hearing loss, and mixed hearing loss may also occur. Symptom onset usually occurs by the early third decade of life, but onset is not unusual later in life. Bilateral form of disease is present in almost 80% of cases (Roland and Samy, 2006). The course of otosclerosis is very variable and so far there are no known factors that could suggest the progression of the disease. However, there are evidence showing that puberty, pregnancy, and menopause hormonal factors could influence the disease progression (Glasscock and Shambaugh, 1990; Donaldson and Snyder, 1993). The otosclerosis is predominantly a Caucasian disease correlating well with their geographic distribution throughout the world and with the mean prevalence estimated at 3/1000 (Karosi et al., 2009). Clinical otosclerosis is very rare among black (1%), oriental and American Indian populations (Guild, 1944). The Japanese and South American populations have half the incidence of that of Caucasians S (Tato and Tato, 1967; Thys et al., 2009). About 60% of the patients with clinical otosclerosis report a family history of the disease. The remaining 40% of cases are either autosomal dominant inherited cases with failure of penetrance in other family members, phenocopies, new mutations or rare cases transmitted with alternate model of inheritance (Thys et al., 2009).

Several medical treatment options have been suggested for otosclerosis, sodium fluoride, NaF (Causse et al., 1982; Bozorg Grayeli et al., 2003), biphosphonates (Keneddy et al., 1993; Quesnel et al., 2012), and bioflavonoids-antioxidants (Sziklai and Ribári, 1995). Nevertheless, the best possible treatment option still remains stapedotomy (Gjurić, 2007).

Despite intensive research the pathophysiology of otosclerosis it still poorly understood. It is current understanding that otosclerosis is a complex disease with different environmental and genetic etiological factors involved. The aim of this paper is to provide a systematic review of the literature concerning the pathophysiology of otosclerosis. Fig. 1.

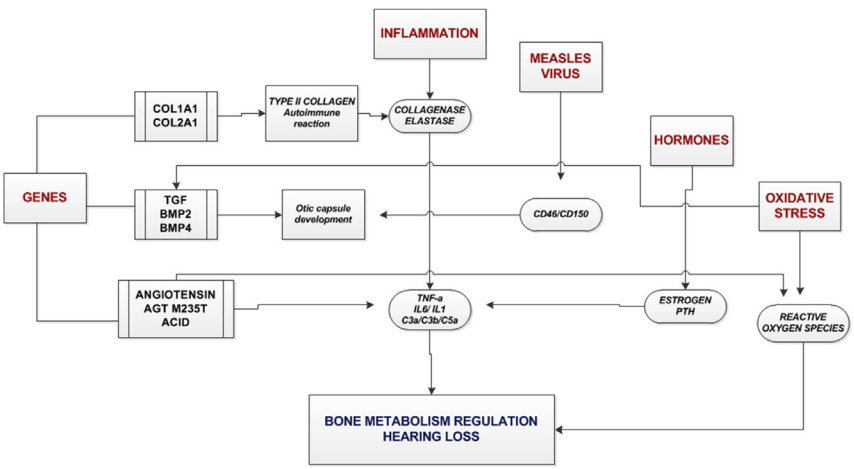

Fig. 1. Schematic diagram showing possible correlation of various etiological factors in otosclerosis. TGF-β (Transgrowing growth factor-β), AGTM235 and ACE I/D (Genetic polymorphisms of Renin Angiotensin Aldosterone System), BMP2/4 (Bone morphogenetic proteins 2 and 4), TNF-α (Tumor necrosis factor-α), IL1/6 (Interleukin 1 and 6), C3a/C3b/C5a (Complement fragments 3a, 3b and 5a), CD46/CD150 (Signaling lymphocytic activation molecules), PTH (Parathyroid hormone), ROS (Reactive oxygen species).

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