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Otosclerosis and Measles Virus – Association or Causation?

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Otosclerosis · Measles virus · Vaccination · Etiopathogenesis · Epidemiology

Abstract
Otosclerosis is a frequent condition which occurs exclusively in the human temporal bone. This peculiar disease affects mainly Caucasians and Indians and may cause conductive, mixed conductive-sensorineural or occasionally merely sensorineural hearing loss. Morphological investigations of the otosclerotic focus show all three phases of a chronic inflammation with bone resorption, formation of new bone and finally eburnation. Various hypotheses about the cause of inflammation were proposed in the past. Immunological reactivity to collagen, the existence of otosclerosis genes (OTSC 1–5) including mutations of the collagen gene 1A1 and 1A2 or a measles virus (MV) infection were suggested. The existence of the MV proteins and RNA within the otosclerotic tissue has been shown by several authors. However, due to mainly technical problems, no further progress to elucidate the role of the virus could be made. Epidemiological studies revealed a dramatic decrease of measles and related diseases such as the subacute sclerosing panencephalitis since the introduction of MV vaccination programs in USA and Europe. Indeed, some surgeons reported decreasing numbers of stapes surgery and a shift towards elder patients. Our epidemiological survey of all patients hospitalized with otosclerosis in Germany between 1993 and 2004 demonstrates a highly significant decrease in otosclerosis among the population vaccinated against the MV. The strong correlation makes it most plausible that the MV is at least one triggering factor for the development of otosclerosis.

Introduction

When in the 17th century the Italian anatomist Antonio Maria Valsalva (Bologna, Italy, 1666–1723) analyzed the temporal bone of a patient supposed to be deaf, he observed a bony fixation of the stapes to the oval window [1]. It took another 100 years before Toynbee revealed ankylosation of the stapes as a cause of hearing loss [2]. Toynbee dissected 1,659 temporal bones and described a fixation of the stapes in 35 samples. Von Tröltsch introduced the term otosclerosis because he believed that middle ear sclerosis could lead to a fixation of the stapes [3]. The first detailed histopathological description of otosclerosis was given through Politzer's microscopical investigation of temporal bones from patients affected by hearing loss [4]. The active phase of otosclerosis was named otospongiosis by Siebenmann in 1912 [5]. The first comprehensive analysis of otosclerosis was published

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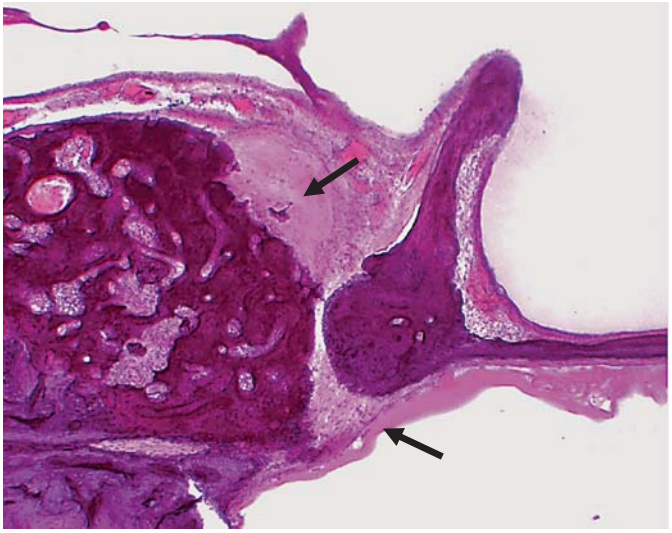

Fig. 1. Otosclerotic focus growing from the promontorium over the annular ligament on the stapes footplate. HE. ×40. Within the thickened fibrous tissue foci of calcification are present (arrows).

by Nager [6] and Ogilvie and Hall [7]. They localized the lesions to distinct topographic regions of the temporal bone such as the globuli interossei and the fissula ante finestram.

Epidemiology of Otosclerosis

Otosclerosis has an important socioeconomic impact because of its high incidence. About 15 million people (6%) in the United States are supposed to suffer from otosclerosis, and as a consequence it is considered to be among the most common causes of acquired deafness [8].

There are two types of otosclerosis according to the localization of the otosclerotic focus. The clinical type is due to a localization of the otosclerotic focus to the oval window niche leading to conductive or mixed conductive and sensorineural hearing loss. In the histological type, which is ten times more frequent, the otosclerotic focus will be in any other region of the temporal bone leading to sensorineural hearing loss, if there are clinical symptoms at all.

Guild investigated 374 consecutive dissected temporal bone specimens and found otosclerotic lesions in 6.5% of men and 12.3% of women [9]. The most comprehensive investigation of temporal bones done so far is that of Hueb et al. [10]. They analyzed 1,452 temporal bones and detected otosclerotic foci in 144 cases. Seifer dissected 601 temporal bones and described an incidence of 8.3% [11]. The last report of about 100 consecutive temporal bones with an incidence of otosclerosis of 3.4% was published by Declau et al. [12]; however, more recent data from large and representative temporal bone studies are not available.

There seem to be sex- and race-specific differences in the incidence of otosclerosis. Otosclerotic foci in the temporal bones are found in 12% of females but only 8% of males [9]. At the level of symptoms, females are affected about twice as often as males. The incidence of otosclerosis among the black population is 10% of that of the white population [8]. Only few data are available from Japanese and African populations, not enough for a comparison. Interestingly, a Japanese study revealed the same frequency of otosclerotic foci within temporal bones as in Caucasians. However, the localization of the foci is less frequent near the oval window, which might explain the rare incidence of clinical otosclerosis among the Japanese population [13].

Genetic factors in the development of otosclerosis have been widely discussed in the literature. The multiple occurrence of otosclerosis within certain families supports this hypothesis [14]. On the background of a genetic predisposition, one or more yet unidentified factors might lead to the development of the characteristic otospongiotic process in the border region between bone and cartilage of the otic capsule. Genetic factors might also account for an enhanced susceptibility to infection by certain viruses. These cells are thought to lie mainly in particular regions such as the globuli interossei. However, in our patients cases where more than one family member suffers from otosclerosis are less frequent. In the last 10 years, several genes have been proposed as a genetic background for the development of otosclerosis. Up to now, 5 otosclerosis genes (OTSC 1–5) have been identified [15]. Furthermore, collagen genes Col 1A1 and Col 1A2 have been discussed as candidate genes in otosclerosis. However, case-control studies could not confirm the presence of any of these genes in patients suffering from otosclerosis [16].

Otosclerosis – A Chronic Inflammatory Disease

Many morphological investigations in the 1980s and 1990s revealed that the otosclerotic focus shows all the characteristics of chronic inflammation (fig. 1) [17]: the

initial (active, lytic) phase of bone resorption with proliferation of blood vessels, osteoclasts and mononuclear cells is followed by the phase of new bone formation. The last inactive stage is characterized by a finally complete obliteration of the lacunae and a dysplastic, compact bone with woven pattern. A detailed immunohistochemical description of the cells within the otosclerotic tissue by Arnold and Friedmann [18], and Altermatt et al. [19] confirmed the presence of an inflammation. Recently, the inflammation-related cytokine TNF-α was reported to be characteristic for otosclerotic tissue but not in the case of nonotosclerotic stapes fixation [20].

Etiopathogenetic Hypothesis

A number of different hypotheses about the origin of this particular chronic inflammatory process were proposed. Mayer [21], and Sercer and Krmpotic [22] believed that the upright walking of humans stresses the temporal bone leading to the inflammation. Ogilvie and Hall [23] considered otosclerosis as a localized form of osteogenesis imperfecta. The clinical association of conductive hearing loss, clinically similar to otosclerosis and blue sclerae is well known as van der Hoeve's syndrome. However, there is no evidence on the clinical level for such an association. Arnold and Plester [24, 25], and Wright [26] suggested the pathological proliferation of vessels which is characteristic for the first stage of disease to be the cause of bone resorption. Causse et al. [27] proposed a disturbance of the trypsin-antitrypsin balance within the otic capsule to be the cause. Recently, mutations of the diastrophic dysplasia sulfate transporter (DTDST) gene were described. DTDST is involved in the regulation of the bone metabolism [28].

Measles Virus Proteins and RNA in Otosclerotic Tissue

In 1976, Mills and Singer [29] described nuclear inclusions in cells from pagetic bone. Other reports about this finding are not available. Because of the histological similarities between Paget's disease and otosclerosis, again McKenna et al. [30] investigated four otospongiotic tissue specimens by electron microscopy. They found in two cases filamentous structures resembling paramyxoviral nucleocapsids in osteoblast-like cells. However, this is a single report only.

Further immunohistochemical investigations of otosclerotic material using monoclonal and polyclonal antibodies against the measles virus (MV) performed by Arnold and Friedmann [31] and McKenna and Mills [32] showed the expression of MV proteins within the inflammatory tissue.

In 1994, we reported the occurrence of MV RNA (genomic and mRNA) amplified from fresh frozen otosclerotic tissue. Stapes footplate samples from patients with clinical otosclerosis were pulverized and after extraction of total RNA MV N sequences could be amplified by RT-PCR in 4 out of 9 samples [33]. These results were confirmed by McKenna et al. [34] who extracted and amplified RNA from formalin-fixed, decalcified and celloidin-embedded temporal bones showing otosclerotic foci. In contrast to our findings and those of McKenna's group, only Bozorg Grayeli et al. [35] were unsuccessful in detecting MV RNA-related sequences when they analyzed RNA extracted from fresh frozen otosclerotic tissue and from (co)cultered cells. Recently, Karosi et al. [36] even described a 100% coincidence between clinical otosclerosis and MV RNA within the pathological tissue.

In addition to the results obtained from otosclerotic tissue, we further described higher percentages of anti-MV IgG in the perilymph of patients with otosclerosis in comparison with the serum levels from the same individuals [37]. Lolov et al. [38] observed that the reactivity of anti-MV IgG of patients with otosclerosis was lower than that of controls. Recently, Karosi et al. [39] even found increased anti-MV antibody titers in serum from patients with otosclerosis. They proposed that in the future the diagnosis of otosclerosis could be made on the basis of serological parameters.

MV Infection

Measles are among the major causes of death by infectious diseases in developing countries [40]. This highly contagious disease seems to be a relatively new human disease. Hippocrates (460–377 BC) recorded herpes labialis and malaria, but there was no account of measles. The Persian physician Abu Becr (10th century) was the first to describe 'eruptions' different from smallpox. Surely up from the 17th century these two diseases were clearly distinguished. The recurrent epidemics were characterized by considerable mortality, and Aztec and Inca civilizations were probably devastated by smallpox and measles in the 16th century.

The introduction of the MV vaccination in the 1970s led to a significant decrease in measles and naturally its complications. However, recently the acceptance of MV vaccination dropped and measles epidemics occur frequently again, even in Germany.

The MV is a typical member of the genus *Morbillivirus* in the family of Paramyxoviridiae. Humans are the only natural host. Infection of monkeys induces a symptom-free development of the disease. The MV has a single-stranded RNA of negative polarity. The virions are spherical, enveloped particles with a helicoidal nucleocapsid. The genome has a size of about 15,900 nucleotides covering six nonoverlapping genes coding for: nucleocapsid, phosphoprotein, matrix, fusion, hemagglutinin and large protein or polymerase [41].

The natural MV infection occurs usually in the acute highly infective form. The MV reaches the epithelial cells of the respiratory tract via aerosol. During the incubation period of 14 days the virus is spread throughout the body. At the time when prodromal symptoms (fever, malaise, anorexia, coryza, conjunctivits and cough) appear, infection is already widely disseminated and lymphatic and epithelial cells show pathologic lesions such as multinucleated cells (Warthin-Finkeldey cell). Measles presents with the symptoms of cutaneous rash, Koplik's spots, and peribronchial interstitial pneumonitis. Complications include acute otits media, pneumonia, acute postinfectious measles encephalitis and keratitis. In immunosuppressed patients, there is the risk for the acute progressive infectious measles encephalitis which takes an acute or subacute fatal course.

On the other hand, MV infection may switch to a latent, persistent infection and several months or years later the chronic disease changes into an acute, subacute or chronic form. This holds for the subacute sclerosing panencephalitis (SSPE) in immunocompetent patients with an insidious onset and a progression to coma over months. The cause of SSPE is a mutated, persistent MV [42]. The reason for the switch from the acute to this persistent form of MV infection is unknown.

MV and Otosclerosis: Consistency of Association

Other chronic diseases such as Crohn's and Paget's diseases are thought to be caused by the MV, and there is accumulating evidence for the notion that the MV is consistently present in otosclerosis [43, 36]. However, it could not be proven so far that the MV actually causes otosclerosis. Only humans and primates are natural hosts of the MV because of their complementary cell surface structures (CD46, CD150).

Further investigations in order to better understand the role of the MV in the development of otosclerosis would require the knowledge of the complete RNA sequence of the MV in otosclerosis, which is currently not known.

The sequencing data of the variable region of the MV N gene amplified from RNA extracted from otosclerotic tissue is of a type which circulated in Europe in the 1960s, and this suggests the presence of a persistent MV infection in otosclerosis [submitted]. Further sequence data are hard to get mainly due to technical problems. For example, extraction of RNA from archival temporal bone tissue reveals only very short gene sequences as shown by McKenna et al. [34]. Furthermore, specimens obtained during stapes surgery are very tiny. Stapes surgery is performed usually in the sclerotic phase and only few cells are present in this otosclerotic bone. As shown by in situ RT-PCR, only few cells contain the MV, which is present in a persistent form. In this phase, gene expression is reduced to a very low level and MV replication occurs at a very low rate. Attempts to isolate the virus by cocultivation have up to now not been successful. Thus, not enough material for RNA extraction is available.

Although several independent authors could detect the MV RNA within the otosclerotic tissue with high score, the MV was never isolated so far despite many attempts. However, a causal role of MV can be accepted for sure only fulfilling Koch's postulates.

Because of these difficulties, other methods to investigate a causal relation between the MV and otosclerosis are required. As for several diseases Koch's postulates do not hold, an alternative had been proposed. Sir Austin Bradford Hill, an English epidemiologist and statistician, pioneered the randomized clinical trial. He was the first to demonstrate the correlation between cigarette smoke and lung cancer. His criteria comprise strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, biological coherence, experimental evidence, and analogy [44].

In the past, several authors from different Western countries reported fewer cases of stapes surgery and a shift towards older patients with otosclerosis [45, 46]. When one postulates that the MV plays a crucial role in the development of otosclerosis, one would expect MV vaccination to have an influence of the incidence of otosclerosis. In Germany, MV vaccination is available since 1974.

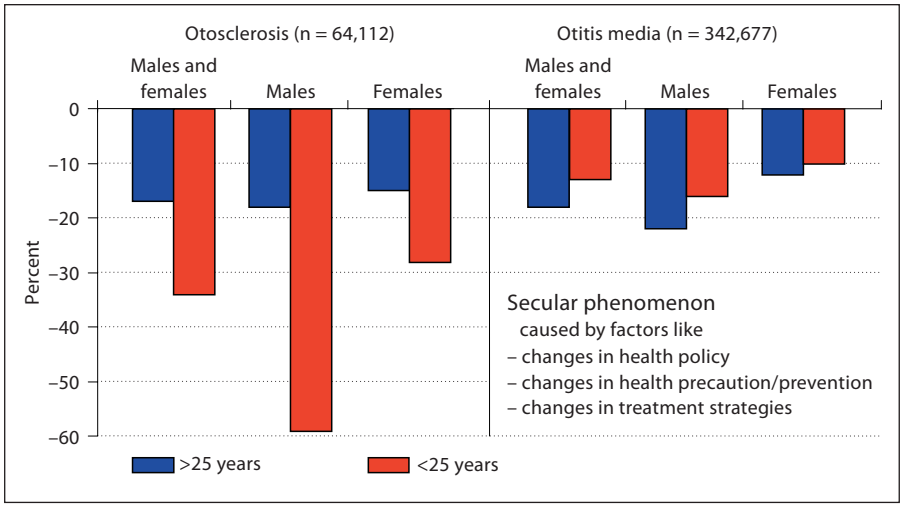

Fig. 2. Comparison of changes of incidence of treatment for otosclerosis and otitis media in male and female inpatients between 1993 and 2004. Patients aged up to 25 years were considered vaccinated, and over 25 years nonvaccinated. The percentages are expressed in comparison with the incidence in 1993. Clear evidence for a significant decrease in the group of patients under 25 years (vaccinated against the MV) with otosclerosis in comparison to the patients with otitis media is given.

Recently, we published our results of all patients that were hospitalized in Germany for otosclerosis from 1993 to 2004 [47]. Summarizing, we analyzed data obtained from the Federal Office of Statistics (Wiesbaden, Germany) based on the International Classification of Diseases (ICD) code (ICD-9: 387; ICD-10: H80) which defines otosclerosis unequivocally. Data from 64,112 patients were collected; the men to women ratio was 1:1.68 (40,219 women and 23,893 men). As external validation, patients with the diagnosis of otitis media (ICD-9: 382; ICD-10: H66; n = 342,766) were included.

Since there was no information on whether the patients were vaccinated against measles or not, two groups were formed: one group of patients born later than 1973 (considered as vaccinated), and the other born before 1973 (considered nonvaccinated). Data about the vaccination rate between 1974 and 2004 were obtained from the Robert Koch Institute and from the literature. We calculated the incidence of otosclerosis and otitis media for the two age groups for each year of the observation period on the basis of the corresponding frequencies and population data obtained from the Robert Koch Institute and the Federal Office of Statistics.

Analysis of the vaccination rate revealed that in 1980 30% and in 1982 65% of all children had been vaccinated against measles at least once. In the following years, the rates went slowly up to 75% in 1992 and peaked in 2004 with 92%.

The overall change of the incidence of otosclerosis revealed a decrease of 45% in the vaccinated group but 13% only in the nonvaccinated group. In the control group, the incidence of otitis media decreased by 13% in the vaccinated group and by 18% in the nonvaccinated patients. A gender-specific analysis revealed that otosclerosis decreased by 61% in vaccinated men and 31% in vaccinated women, whereas otitis media in 13% of nonvaccinated men and 12% of nonvaccinated women only. In the control group, the incidence of inpatient treatment decreased by 16% in vaccinated males and 10% in vaccinated females, while in the nonvaccinated group the decrease was 23% for men and 11% for women (fig. 2).

There is a statistically significant decrease in otosclerosis in the vaccinated patients in comparison with nonvaccinated patients. There is also a decrease in the incidence of otitis media, but the decrease there is smaller in the vaccinated group than in the nonvaccinated group. Furthermore, the decrease in the percentage of patients with otitis media, both vaccinated and nonvaccinated, is similar to that of the nonvaccinated otosclerosis group. This general decrease observed in all patients with otitis media, vaccinated against MV or not, and in the nonvaccinated patients with otosclerosis might be due to various (e.g. socioeconomical) factors as observed in several diseases. This phenomenon is known as centennial phenomenon.

Finally, the minor decrease in otosclerosis in the vaccinated female group in comparison with the vaccinated male group might indicate gender-specific differences in susceptibility or reactivity to MV. In accordance to this result, several authors described the occurrence of more severe clinical measles and a higher rate of complications after MV vaccination in women than in men [48].

Compared to measles which dropped down dramatically since the introduction of MV vaccination, otoscle-

Table 1. Bradford Hill's criteria: measles virus and otosclerosis

Strength of association	Measles virus proteins and RNA were detected by independent authors in 66–100% of otosclerotic tissue in Europe and USA.
Consistency	More than 30 independent studies have shown by several techniques the presence of measles virus proteins and RNA sequences.
Specificity	Measles virus proteins and RNA sequences were shown in the affected otosclerotic bone but not in control tissue.
Temporality	Measles virus infection occurs in children and otosclerosis develops several years later.
Biological gradient	Little is known about the dose dependence of measles virus on the development of otosclerosis. Measles virus is highly infective and after viral exposure measles occurs consistently in the nonvaccinated population.
Biological plausibility	Immunohistochemical investigations showed a chronic inflammation in the otosclerotic focus. CT scan of the temporal bone with otosclerosis reveals foci of bone resorption or new bone formation.
Biological coherence	Otosclerosis is shown to occur as a chronic inflammatory disease. As triggering factor a virus does not conflict.
Experimental evidence	In vitro and in vivo evidence supports a causal role of measles virus in otosclerosis.
Analogy	Other paramyxoviruses can induce chronic inflammatory diseases. A persistent measles virus infection causes SSPE.

rosis in the vaccinated group only decreased by 45%. As mentioned before, measles are an acute inflammatory disease while otosclerosis is a chronic inflammatory disease which develops over several years or decades. Furthermore, it is accepted that 5% of MV vaccinated patients are nonresponders [49]. Finally, epidemiological investigations have shown that a single MV vaccination may not protect efficiently against a MV infection. Therefore, a second administration of the vaccine has been recommended since 1991 [50].

Conclusion

Many investigations revealed the presence of MV proteins and RNA within the otosclerotic tissue. The MV in otosclerosis was demonstrated to be of a persistent type. Since the introduction of MV vaccination one could register a shift towards older patients with otosclerosis and a significant decrease of this condition in younger patients. All the data we looked at met the criteria of Sir Austin Bradford Hill (table 1). We suggest that the development of otosclerosis is triggered by a persistent MV infection and that the MV vaccination could prevent otosclerosis to a certain extent.

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Comments

J.R. García-Berrocal: The authors investigate a causal relation between the MV and otosclerosis. The presence of MV proteins and RNA and the chronic inflammatory response observed within the otosclerotic tissue support the hypothesis of the present study. Consistency of the association is also based on the decreased incidence of otosclerosis in the group of presumed vaccinated patients when compared with the nonvaccinated patients. Naturally, such attractive hypothesis states that the MV vaccination could prevent otosclerosis at least to a certain

extent. Even though a proper vaccination program was performed, a low percentage of patients could suffer measles. Obviously, the nonvaccinated population would suffer a chronic latent MV infection and thereby serological tests and MV isolation in otosclerotic tissue obtained from surgical specimens of nonvaccinated patients could provide another proof to support the hypothesis.

However, some questions require further investigations: Are there any other viruses involved in otosclerosis etiopathogenesis? Does the host immune response influence the latent infection of the otosclerotic tissue? Can otosclerosis represent a reactivation of a subclinical MV infection?

T. Linder: Niedermeyer and Arnold present a comprehensive and carefully considered review of the possible etiopathogenesis of MV infection and otosclerosis. Although viral particles and RNA fragments have been identified by different authors (although most publications appear to be from the same laboratories; the diversity appears to be less than in e.g. otitis media research), there still is some doubt regarding the exact pathogenesis of a MV latent infection within the otic capsula. The epidemiologic study needs to be analyzed cautiously. Since no exact information was available on whether the patients had been vaccinated at all, only once or even twice, the statistical analysis was based on a mere assumption on the overall vaccination habits in Germany within the years examined. We also do not know the incubation time, e.g. the time needed between the infection and the clinical signs of otosclerosis, making any correlation with the overall vaccination practice even more difficult. Many of our patients operated for otosclerosis have had the recommended MMR vaccine in early childhood and still developed the disease. Interestingly, no other reports have dealt with the vaccination status of otosclerosis patients, actually quite an easy question to be answered. Karosi et al. [39] published a series of papers verifying the viral etiology and are also mentioned in the text. Interestingly Niedermeyer cited their results as follows: 'Recently, Karosi et al. [39] even found increased anti-MV antibody titers in serum from patients with otosclerosis.' But actually the contrary is true: Low antimeasles IgG level indicated otosclerosis, whereas high level suggested nonotosclerotic ossicular chain fixations. Antimeasles IgG levels were significantly lower in the sera of patients with virus-positive stapes (141 out of 213 clinically fixed stapes) than in control sera. Therefore, the hypothesis just reverses: less antibody response, more otosclerosis. It would also be tempting to presume: more antibody response, more infection and more otosclerosis. The answer has yet to be determined.

C.A. Oliveira: Two questions come to mind regarding this issue. The first one is: Is the MV the only one that has RNA in the otosclerosis lesion? Have other viruses been investigated? The second question refers to the epidemiologic argument. Even though we do not have reliable numbers, it is reasonable to say that the prevalence of measles in countries like Brazil was much higher than in developed countries before the vaccination. Yet, otosclerosis has always been much less frequent in Brazil than in Europe and the USA. This can only be explained by genetic differences between the Brazilian population with strong African and Indian background and the predominantly Caucasian population of Europe and the USA. These genetic differences overshadow the high prevalence of measles in Brazil before the vaccination. The most one could say is that the MV can trigger the otosclerotic process in some genetically predisposed patients.

I. Pyykkö: The evidence for the role of the MV in the etiology of otosclerosis indicates that there is an association between MV and otosclerosis. Also impressive was the statistics showing a reduction of otosclerosis after the introduction of MV vaccination. There is also a strong genetic component in the etiology of otosclerosis and no data are available for the expression of illness in members of genetically susceptible families. The genetic part may consist of a separate disease entity and use different mechanisms to develop otosclerosis. Furthermore, it is difficult to explain the latency of otosclerosis onset in middle age when the MV infection occurs at young age.