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Review

Meniere's disease might be an autoimmune condition?

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ABSTRACT

Objectives: To review our current knowledge of the pathogenesis of Meniere's disease, including viral infection and immune system-mediated mechanisms, and to discuss the pathogenesis as it relates to pharmacotherapy.
Systematic review methodology: Relevant publications on the aetiopathogenesis, molecular biology, genetics and histopathology of Meniere's disease from 1861 to 2011 were analysed.
Results and conclusions: Meniere's disease is characterised by intermittent episodes of vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural pressure. The aetiology and pathogenesis remain unknown. Proposed theories of causation include viral infections and immune system-mediated mechanisms. The immune response in Meniere's disease is focused on inner ear antigens. Approximately one-third of Meniere's disease cases seem to be of an autoimmune origin although the immunological mechanisms involved are not clear. The diagnosis of autoimmune inner ear disease is based either on clinical criteria or on a positive response to steroids. The antiviral approach has virtually eliminated the use of various surgical methods used in the past. Steroid responsiveness is high, and with prompt treatment, inner ear damage may be reversible. The administration of etanercept improves or stabilises symptoms in treated patients. Treatment of antiphospholipid syndrome can be directed toward preventing thromboembolic events by using antithrombotic medications. Only warfarin has been shown to be effective. Gene therapy can be used to transfer genetic material into inner ear cells using viral vectors and to protect, rescue, and even regenerate hair cells of the inner ear.

Contents

1. Introduction

Prosper Meniere first described Meniere's disease in 1861 [1]. He challenged the general terminology at the time that called this disease apoplectic cerebral congestion, implying a disorder of the brain. Meniere described this pathology as being associated with the peripheral end organ of the inner ear rather than the brain. He and other investigators called it "glaucoma of the ear" [2,3].

In 1927, Guild [4] identified the endolymphatic sac as the site of the "outflow of endolymph". Later that same year, Portmann [3] described his first endolymphatic sac surgery for Meniere's disease. The following year, in 1928, Dandy [5] proceeded with vestibular neurectomy, which attempted to isolate the vestibular system from the brain and thus cure patients of vertigo. In 1943, Altmann and Fowler [6] concluded that problems in production and absorption of endolymph can lead to Meniere's disease. In a landmark study in 1967, Kimura [7] developed the first animal model using guinea pigs and showed that blockage of the endolymphatic sac and duct causes obstruction of endolymphatic outflow, leading to hydrops of the inner ear.

Meniere's disease remains a difficult disease to diagnose, especially in the early stages when not all of the symptoms may be present. Few articles have been published on the epidemiology of Meniere's disease. In 1973, Stahle and colleagues reported a prevalence of 46 cases per 100,000 people [8]. From 1975, several studies indicated a prevalence

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of 17 cases per 100,000 people [9,10]. Kotimaki and colleagues reported a prevalence of 43 per 100,000 and an average yearly incidence of 4–3 per 100,000 people in the population [11]. Most studies suggest a female preponderance of up to 1–3 times that in men. The disease seems to be much more common in adults in their fourth and fifth decades than in younger people, although it has been reported to occur in children [12]. A strong positive family history exists in patients with Meniere's disease. Several studies have indicated that up to 20% of family members have similar symptoms [13,14].

Meniere's disease is characterised by intermittent episodes of vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural pressure [15]. It has been classified into typical Meniere's disease, with all the before mentioned cochlear and vestibular symptoms, and atypical Meniere's disease, with either cochlear symptoms (e.g. hearing loss, tinnitus and aural pressure) or vestibular symptoms (e.g. vertigo with aural pressure) [16].

1.1. Pathophysiology

The primary histopathological correlate of Meniere's disease is endolymphatic hydrops. Paparella used the notion of a "lake, river, and pond" to explain the occurrence of malabsorption of endolymph leading to hydrops [15]. This notion describes the endolymphatic sac as a pond, the vestibular aqueduct as a river, and the endolymphatic fluid space as a lake. When there is an obstruction near the endolymphatic sac or duct, a backlog of endolymphatic fluid is created, leading to hydrops.

The first temporal bone histopathological studies of Meniere's disease by Hallpike, Cairns [16,17] and Yamakawa [18] reported a ballooning distension of the endolymphatic system, a finding that is almost invariably seen in documented Meniere's disease [19,20]. Previous temporal bone studies demonstrated evidence for endolymphatic membrane rupture or fibrosis around the endolymphatic sac; however, further temporal bone studies did not provide evidence for fibrosis of the endolymphatic sac [21].

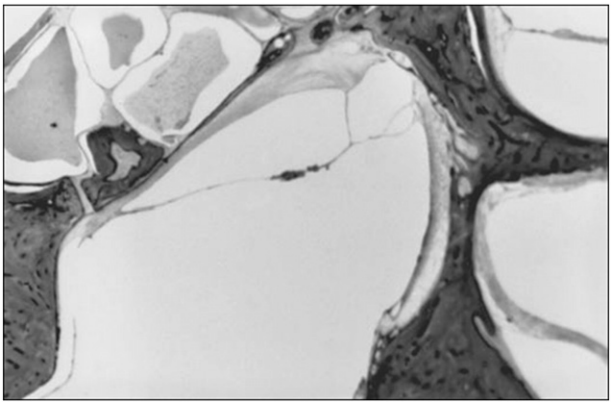
Vestibular fibrosis between the saccular wall and the stapes footplate has been observed in 35% of human temporal bones extracted from Meniere's disease patients (Picture 1) [20–22]. A recent human temporal bone study [19] suggested that the endolymphatic hydrops in Meniere's disease is "a marker for a disordered homeostasis of the labyrinth in which some factor (as yet unknown) produces both the clinical symptoms of Meniere's syndrome and endolymphatic hydrops".

Furthermore, primary and secondary endolymphatic hydrops have been documented in the temporal bones of subjects without symptoms of Meniere's disease [19]; thus, hydrops is likely an epiphenomenon. Previous histopathological studies of surgically obtained endorgans from Meniere's disease patients at the light microscopic level have posited a relative preservation of the vestibular neuroepithelium [20,23,24]. In many prior studies, though, only the utricular macula was systematically evaluated. More recently, it was found that the majority of the vestibular endorgans demonstrated variable degrees of neuroepithelial degeneration, including conversion of the sensory epithelium to a monolayer, basement membrane thickening, cellular vacuolisation, absence of hair cell stereocilia, and increased intercellular stromal space. The utricular macula was relatively spared (Picture 2) [25].

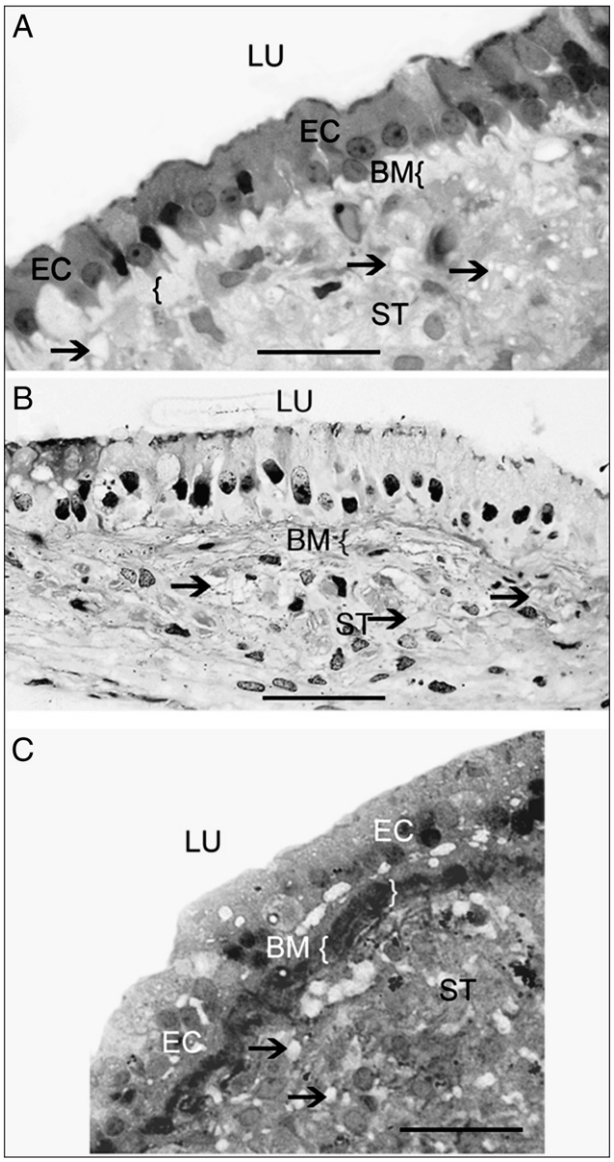
The pathogenesis of Meniere's disease is still unknown; however, it has been proposed that viral infections and autoimmune processes may play a role in the induction of the disease.

1.2. Viral hypothesis

Endolymphatic hydrops of the membranous labyrinth has been recognised as the pathological correlate of Meniere's disease for over 70 years [17,18]. Obstruction of endolymph flow has been implicated



Picture 1. Horizontal section through the vestibule of patient demonstrates fibrous tissue (*) surrounding a dilated saccular wall (arrow heads) under the stapes footplate (F). S = Saccular macula (Gacek RR. Meniere's disease is a viral neuropathy. ORL 2009; 71: 78–86.).



Picture 2. Sensory epithelia from Meniere's disease vestibular endorgans. (Mc Call AA, Ishiyama GP, Lopez IA, Bhuta S, Vetter S, Ishiyama A. Histopathological and ultrastructural analysis of vestibular endorgans in Meniere's disease reveals basement membrane pathology. BMC Ear Nose Throat Disorders 2009; 3; 9: 4.).

as the cause of endolymphatic hydrops [26,27]. Significant questions to this proposed pathophysiological mechanism persist. First, although endolymphatic hydrops is readily produced by surgical obliteration of the endolymphatic sac in lower organisms (guinea pig, chinchilla, gerbil), it does not occur in higher mammals (cat, monkey) [28]. Second, imbalance (vertigo) has not been observed in these animal models. Third, the temporal bones of animal models with experimentally induced endolymphatic hydrops do not contain fibrous tissue adjacent to the stapes footplate with attachment to the saccular wall.

Viral infection has been advocated as a possible cause of Meniere's disease by many authors [29,30]. It has also been postulated that certain viruses have more affinity than others for affecting the inner ear [31]. For this reason, many studies have been carried out to verify whether viruses such as the neurotropic viruses, herpes simplex virus (HSV) types 1 and 2 [32], varicella zoster virus (VZV), and cytomegalovirus (CMV) [33], can cause Meniere's disease by invading the endolymphatic sac. The endolymphatic sac is known to be the site of immune reaction due to the existence of lymphocytes and immunoglobulins in addition to the resorption of endolymphatic fluid [34,35].

Traditionally, to prove that a clinical syndrome is caused by an organism, Koch's postulates must be satisfied. While such an approach is possible for bacterial and some viral organisms, the neurotropic viruses belonging to the Herpesviridae family do not lend themselves to this approach because the virus exists in an incomplete latent form within the cell nucleus with a brief period of recrudescence when the virion is formed [36,37], making detection difficult. Attempts to identify the presence of viruses in the inner ear have generally been based on immunohistochemical examinations for viral antigens [38] and serum viral antibody titres.

Arnold and Niedermeyer [32] evaluated the presence of higher IgG antibodies against herpes simplex virus (HSV) in the perilymph of patients with Meniere's disease. This result supported the hypothesis that the herpes simplex virus may play an important role in the aetiopathogenesis of Meniere's disease. Higher titres of IgG against adenovirus (ADV) and varicella zoster virus (VZV) were found in patients with Meniere's disease compared with a control group. These findings support the hypothesis that adenovirus and varicella zoster virus may be important in the development of Meniere's disease [39].

The mechanism by which viral infection can cause Meniere's disease is different, due to the large variability between the viruses and host antigens. First, the viruses must have an affinity for the inner ear structures. Second, viral invasion of the endolymphatic sac is impeded by immunological mechanisms under normal conditions [40]. The antigen may be present at all times but hidden from the host's immune system unless there is an active viral infection. Release or exposure of the virus may occur as a result of cell damage or destruction during viral infection. Such previously sequestered antigens would be recognised as foreign by the host, and the resulting immune response may lead to the production of autoantibodies and possibly to a further cycle of tissue damage through autoimmunity.

A possible source of the chemical injury to the labyrinth could be the release of infectious nucleic acids from vestibular nerve terminals following reactivation of the virus in the vestibular ganglion. Such nucleic acids have a level of infectivity unlike that of a live virus, but are neutralised by the release of nucleases by blood components [41]. The hypothesis that Meniere's disease is a viral neuropathy is supported by the significant loss of vestibular ganglion cells compared to age-matched temporal bones [42,43]. Reactivation of the latent neurotropic virus is dependent on viral load [44].When the viral load reaches a critical level, reactivation of the virus overcomes the host immune response with the release of viral nucleic acids. Release of such toxic products in the labyrinth causes a labyrinthitis, which eventually leads to fibrosis in the vestibular cistern and endolymphatic hydrops.

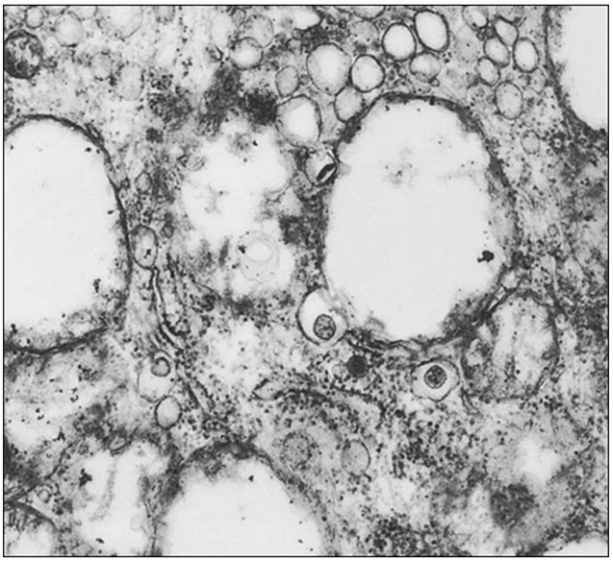
Recently, direct evidence of viral neuropathy in Meniere's disease has been provided by the transmission electron microscopic observation of viral structures in vestibular ganglion cells excised from a patient with Meniere's disease (Picturess 3 and 4) [45,46]. The clinical response to antiviral medication indicated that vertigo due to Meniere's disease was relieved in 85–90% of patients. It is not surprising that control of vertigo was not greater than 85–90%, as mutant strains of the herpes virus group would be resistant to the acyclovir class of antivirals. Until newer antivirals are developed, approximately 10% of Meniere's disease patients with vertigo will not be controlled. The auditory symptoms are less effectively treated by the antiviral approach because loss of hair cells and spiral ganglion cells secondary to the toxicity of viral proteins in the perilymph is not reversible.

Side effects of acyclovir administration are minimal and usually involve gastrointestinal tract hyperactivity, which is eased by decreasing the dosage. Acyclovir is used based on expense. Valtrex or Farmvir have better bioavailability but are significantly more expensive. Rare side effects are skin rash, headache or tremors. If these occur, the patient may require other options to control his or her vertigo, such as intratympanic instillation of antivirals (Ganciclovir). No increase in side effects or viral resistance has been reported when using maintenance doses for long-term (decades) periods (Acyclovir 800 mg or Valtrex 1 g daily) [46].

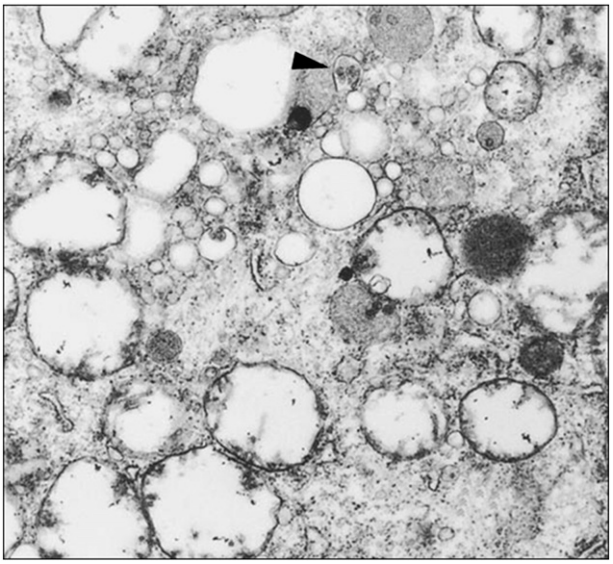
1.3. Immunologic theory

The concept that the immune system may have a role in some idiopathic hearing loss and vestibular disorders was introduced during the early decades of the past century by Joannovic [47] and Masugi [48]. In 1958, Lehnhardt [49] suspected that certain cases of sudden bilateral hearing loss could be related to the production of anticochlear antibodies. Kikuchi [50] proposed an autoimmune aetiology after observing that surgery on one ear affected the other ear. Beickert [51], in 1961, and Terayama [52], 3 years later, both presented data supporting an autoimmune mechanism in experimental guinea pig cochleae.

In 1979, McCabe [53] first described patients with bilateral progressive hearing loss that responded to steroid therapy. The clinical presentation of sensorineural hearing loss can be quite variable, often overlapping with other disorders such as Meniere's disease. Hughes et al. [54] reported that over 52% of patients diagnosed with autoimmune inner ear disease presented with hearing loss and vertigo. This suggests that a continuum may exist between Meniere's disease and sensorineural hearing loss. Today, there is vast evidence of autoimmune



Picture 3. Virion particles (arrows) were present in transport vesicles of vestibular ganglion cells excised from patient with Meniere's disease. M = Mitochondria. Original magnification ×13,000. (Gacek RR. Meniere's disease is a viral neuropathy. ORL 2009; 71: 78–86.).



Picture 4. Virus invaginating transport vesicle in vestibular ganglion cells. (Gacek RR. Meniere's disease is a viral neuropathy. ORL 2009; 71: 78–86.).

mechanisms in some of the inner ear disease entities, including Meniere's disease, otosclerosis, progressive sensorineural hearing loss and sudden deafness.

Approximately one-third of Meniere's disease cases seem to be of an autoimmune origin, although the immunological mechanisms involved are not clear [55,56]. There are several theories as to how autoimmune inner ear disease might arise:

- Cross-reactions: antibodies or rogue T cells cause accidental inner ear damage because the ear shares common antigens with a potentially harmful substance, virus or bacteria that the body is fighting. This is presently the favoured theory of autoimmune inner ear disease.
- Bystander damage: damage to the inner ear causes cytokines to be released, which provoke (after a delay) additional immune reactions. This theory might explain the attack/remission cycle of disorders such as Meniere's disease.
- Intolerance: the body may not know about all of the inner ear antigens. When they are released (perhaps following surgery or an infection), the body may wrongly mount an attack on the "foreign" antigen. In the eye, there is a syndrome called sympathetic ophthalmia, whereby, following a penetrating injury to one eye, the other eye may go blind. In the ear, the same mechanism could be involved in the so called sympathetic cochleo-labyrinthitis that has been reproduced in animal models [57].
- Genetic factors: genetically controlled aspects of the immune system may increase or otherwise be associated with increased susceptibility to common hearing disorders, such as Meniere's disease. Bernstein et al. [58] reported that 44% of patients with Meniere's disease had one particular extended major histocompatibility complex (MHC) haplotype (Dqw2-Dr3-c4Bsf-C4A0-G11: 15-Bf:0.4-C2a-HSP70:7.5-TNF), compared to only 7% of controls.

According to others authors, autoimmunity seems to be responsible for 6% of unilateral and 16% of bilateral forms of Meniere's disease [59]. This hypothesis is supported by ample experimental data:

1) Hydrops can be induced experimentally by injection of antigens or monoclonal antibodies [60].
2) Inner ear antigens with molecular weights of 68 kDa, 58 kDa, 42 kDa and 28 kDa might be the main components inducing autoimmune Meniere's disease in guinea pigs [61].
3) The deposition of circulating immune complexes may produce inflammation and interfere with the capability of the endolymphatic sac's filtering. Several studies demonstrated increased values of circulating immune complexes in 21% to 96% of patients with Meniere's disease [62].
4) Antiviral antibodies and lymphocyte blastogenesis have all been demonstrated [63].
5) The endolymphatic sac is the site of the immune response of the inner ear and is also the site mostly involved in the pathogenesis of Meniere's disease [64].

Recently, various groups have focused their attention on the immune response to inner ear antigens, and a number of studies have sought to identify these autoantigens. Wei et al. [65] found antibodies reactive with autologous ganglion cells in Meniere's disease patients. They suggested that alterations in the microvasculature, due to an autoimmune reaction in the spiral ganglion, could trigger Meniere's disease. Increased levels of anti-collagen II antibodies have also been reported in a high percentage of Meniere's disease patients by Yoo et al. [66,67].

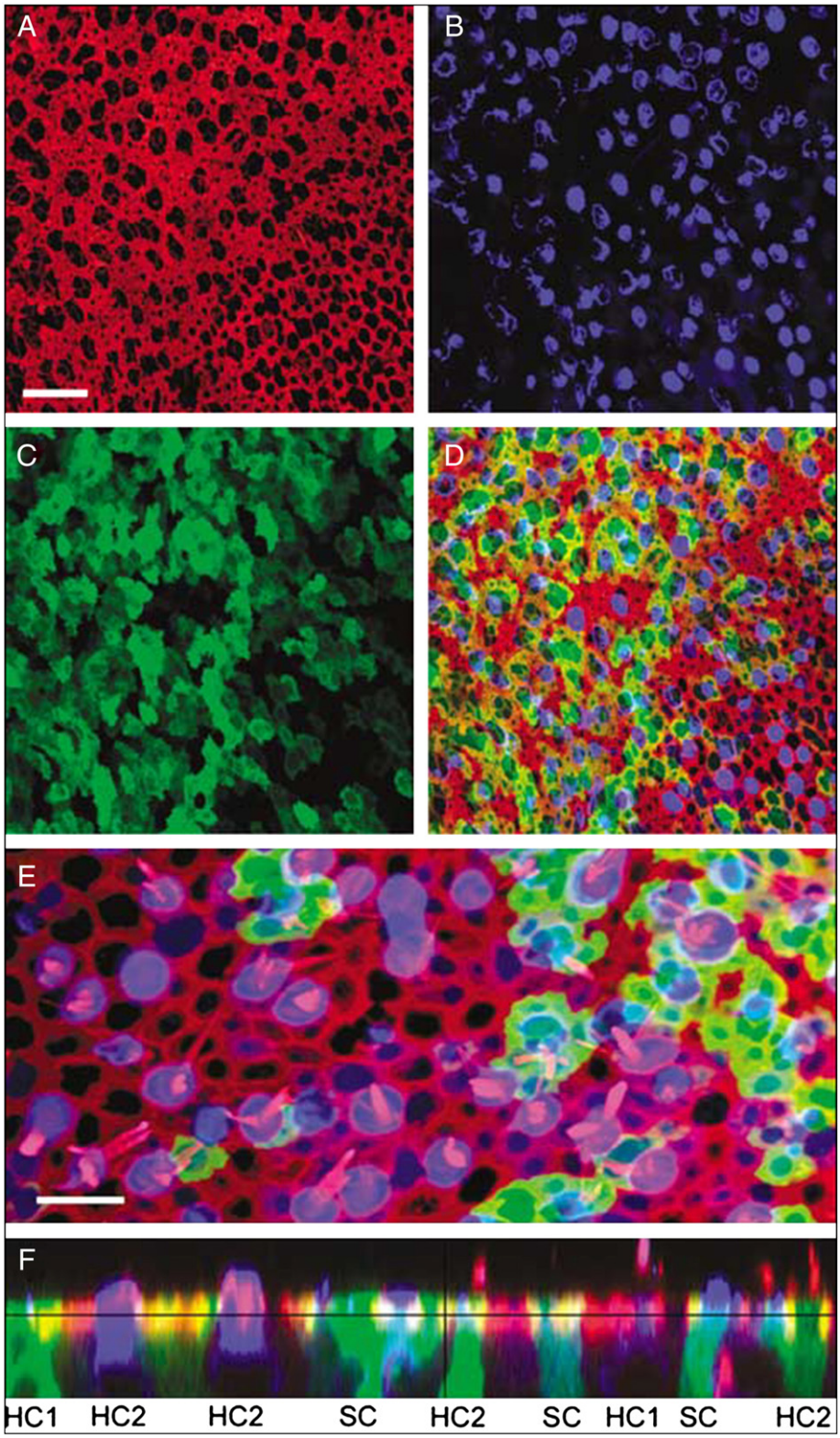
Patients with autoimmune inner ear disease frequently react with another ubiquitous protein of 42 kDa that has been identified as beta actin [68]. As reviewed by Yoo et al. [69], the antigens most commonly detected by patient's sera with autoimmune inner ear diseases are 32–35 kDa, 42–46 kDa, 52–58 kDa, 57–68 kDa and 79–80 kDa. These antigens have been detected in different species, suggesting once again that organ-specific and not species-specific antigens are the target of autoantibodies.

It has long been speculated that Meniere's disease might be an immune-mediated or even an autoimmune condition [69]. Anti-heat shock protein 70 (HPS70) antibody, tumour necrosis factor (TNF)-alpha, antinuclear antibody (ANA), anti-phospholipid antibodies, and erythrocyte sedimentation rate (ESR) are immunologic parameters that have been studied for possible association with autoimmunity in Meniere's disease. Corticosteroid therapy has frequently been used in Meniere's disease. Diagnosis of autoimmune inner ear disorders is still largely based on the response to steroid therapy.

Many studies have demonstrated circulating antibodies against antigens in bovine inner ear extracts in patients with Meniere's disease. One such target antigen that was believed to be specific to the inner ear is a 68 kDa protein, but it was proved to be a heat shock protein (HSP) that was also expressed in cells of other tissues [70]. HSPs are immunogenic and capable of inducing a species-specific immune response. An inner ear HSP 70 becomes immunogenic because of over-expression secondary to inflammation caused by another agent and causes cochlear dysfunction through an autoimmune reaction in which a cellular immune response plays a central role [71]. The presence of antibodies to a 68 kDa antigen, identified by Western blot, has been shown in sera of up to 73% of patients with Meniere's disease in some studies [72,73]. Western blotting is the first step in antigen identification; in fact, the molecular weight is only one of the many features that define a protein, and a number of antigens from the same tissue may share an identical molecular weight. Thus, only the biochemical characterisation of these inner ear autoantigens can shed more light on the pathogenetic mechanisms of Meniere's disease [74].

In the last decade, new molecules have been investigated to identify the role of cytokines in autoimmune diseases. Also, new drugs are being developed to interfere with cytokines. TNF-alpha is a cytokine that induces the infiltration of immunocompetent cells into the tissues and amplifies the immune response. In an experimental model of labyrinthitis, the TNF-alpha blocker, Etanercept, was shown to reduce the amount of inflammation in guinea pigs [75]. Encouraging results in a clinical study have shown that the administration of Etanercept to patients with immune-mediated inner ear diseases, including MD patients, improved or stabilised symptoms in 50% of treated patients [76].

A statistically significant elevation in the levels of antiphospholipid antibodies has been demonstrated in patients with Meniere's disease



Picture 5. Confocal images of a saccule harvested from a patient (Kesser BW, Hashisaki GT, Fletcher K, Eppard H, Holt JR. An in vitro model system to study gene therapy in the human inner ear. Gene Ther 2007; 14: 1121–1131.).

[77]. The pathology mediated by antiphospholipid antibodies is best understood by analysing the vessels involved and the time course of the thrombotic process [78]. Depending on the size of the vessel affected, organ failure has two predominant causes, thrombotic microangiopathy or ischaemia secondary to thromboembolic events. With regard to the pathogenesis of isolated inner ear disease, it would be reasonable to hypothesise that these antibodies would affect the small vessels of the labyrinthine circulation. Antiphospholipid antibodies could activate endothelial cells directly or by inducing the formation of free radicals that secondarily damage the endothelium. These endothelial cells would initiate local micro-thrombus formation and subsequent ischaemia of the end organ [78].

Treatment of antiphospholipid syndrome can be directed toward preventing thromboembolic events by using antithrombotic medications and toward modulating the immune response with immunotherapy. Of these medications, only warfarin has been shown to definitively be effective [78]. It is believed that glucocorticoid therapy, in addition to its anti-inflammatory effects, may also protect neural tissues from ischaemic injury and stabilise the vascular endothelium [79]. These data support the hypothesis that antiphospholipid antibodies are involved in the pathogenesis of some forms of inner ear dysfunction, presumably by causing microthrombus formation in the labyrinthine vasculature. Basic science studies are required to better understand the mechanisms by which antiphospholipid antibodies may mediate inner ear dysfunction. Clinical studies to evaluate the efficacy of anticoagulation in Meniere's disease patients are also required.

On the contrary, antibodies to ubiquitous antigens, which are commonly recognised by systemic autoimmune disease sera, are not present in Meniere's disease patients. At the same time, signs and symptoms of autoimmune disorders are not present in these patients, and significant associations with connective tissue disorders have not been found. The results obtained in many studies suggest that the immune response in Meniere's disease is focused on inner ear antigens. It remains unclear whether the antibodies to these antigens play a role in the pathogenesis of Meniere's disease or if they represent the result of inflammation and tissue destruction. Even if the latter is the case, they could contribute to the perpetuation of the disease.

While specific tests for autoimmunity to the inner ear would be desirable, there are currently none that are both commercially available and proven to be useful. Nonetheless, despite the stronger evidence that immune mechanisms are involved in the aetiopathogenesis of inner ear damage, there are few tests available for the specific diagnosis of autoimmune disorders. At the same time, steroid responsiveness is high, and with prompt treatment, inner ear damage may be reversible. Currently, the diagnosis of autoimmune inner ear disease is based either on clinical criteria or on a positive response to steroids.

2. Conclusions

Meniere's disease is still an obscure disease entity, even though it was first described more than 150 years ago. Its clinical features are currently well known, but its aetiology is still unclear; determining that aetiology is considered a great challenge. The treatment of Meniere's disease is still based on incomplete knowledge about the underlying pathophysiology. It is true that we still do not have a cure for this disease, as with many other illnesses in medicine. The fact that so many patients with recurrent vertigo are referred because of the ineffectiveness of diuretics, low salt diets, and vestibular suppressants (Meclizine, Diazepam) indicates that the currently employed medical management of recurrent dizziness needs to be changed.

The antiviral approach to the very common disabling balance symptoms experienced by patients with Meniere's disease has virtually eliminated the use of various surgical methods used in the past. These include labyrinthectomy, endolymphatic sac decompression and vestibular nerve transection. The high (90%) rate of vertigo control with orally administered antivirals should be considered as a frontline treatment for vertigo.

TNF-alpha blockers (Etanercept) could play a role in the treatment of Meniere's disease in the future [80]. At the same time, steroid responsiveness is high, and with prompt treatment, inner ear damage may be reversible. If patients do not respond to the oral steroids, intratympanic injection can be given. Diagnosis of autoimmune inner ear disorders is still based on the response to steroid therapy. The cure for this disease is yet to be discovered, but it could lie in genetic re-engineering that might require a functioning labyrinth for an effective outcome. Therefore, destructive procedures like transtympanic perfusion of Gentamicin, which might preclude a possible cure for patients in the future, should be avoided. Gentamicin causes direct damage to the sensorineural epithelium of the labyrinth, thus affecting vestibular and cochlear function. It would be prudent for us to continue to be conservative by preserving the structures of the inner ear and working to alleviate patient symptoms without destroying these structures, as much as possible.

Gene therapy has been characterised over the last decade and can be used to transfer genetic material into inner ear cells using viral vectors. The addition of a segment of genetic material into a cell results in the expression of a protein and ultimately a change in the function of the cell. Several viral vectors, including adenovirus [81,82], adeno-associated virus [83,84], herpes simplex virus [85,86], and other viruses, have been shown to transfect various cell types of the mammalian inner ear. Viral-mediated gene therapy may be developed as an important tool for treating genetic forms of hearing loss and balance dysfunction.

Theoretically, and now experimentally, gene therapy can be used to alter the cellular microenvironment of the inner ear as well as change the cellular phenotype to protect, preserve, rescue, and even regenerate hair cells [87].

In the developing organism, hair cells and supporting cells arise from a common progenitor cell [88]. In birds and reptiles, injured hair cells are replaced via differentiation of supporting cells into new hair cells [89,90]. Mammalian hair cells, on the contrary, are terminally differentiated, and hair cell loss is irreversible. Recently, Kesser et al. [91] characterised adenovirus-driven expression of a reporter gene (green fluorescent protein [GFP]) and a functionally relevant gene (KCNQ4) into cultured human vestibular epithelia. This represents an important step toward demonstrating applicability of gene transfer to treat human inner ear disease (Picture 5).

Challenges for the future of inner ear gene therapy include refining vectors to improve transfection efficiency and cell targeting, refining methods of delivery to minimise trauma to the inner ear while ensuring widespread transfection of the inner ear [92], and discovering new genes whose replacement or silencing may restore function [93]. With the discovery that human vestibular epithelia can be transfected with a virus, human hair cells can now be accessed with various experimental manipulations. This platform can be used to test viral vectors, neurotrophic factors, stem cell candidates, and other pharmacologic agents designed to treat human inner ear dysfunction [87].

Take-home messages

- Meniere's disease is an autoimmune disorder. Its etiopathogenesis includes viral infection. The histopathological correlate of Meniere's disease is endolymphatic hydrops and vestibular endorgans demonstrates variable degrees of neuroepithelial degeneration
- Due to the possible autoimmune pathogenesis of the disease, pharmacotherapy for Meniere's disease may include corticosteroids, etanercept and warfarin. The use of antiviral agents corresponds to the viral hypothesis and has eliminated the various surgical methods of the past.
- Gene therapy could be used in the future to transfer genetic material into inner ear cells using viral vectors and to protect, rescue, and even regenerate hair cells of the inner ear

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Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism

MgSO(4) exposure before preterm birth is neuroprotective, reducing the risk of cerebral palsy and major motor dysfunction. Neonatal inflammatory cytokine levels correlate with neurologic outcome, leading **Sugimoto J. et al. (J Immunol 2012; 188(12): 6338-46**) to assess the effect of MgSO(4) on cytokine production in humans. They found reduced maternal TNF-α and IL-6 production following in vivo MgSO(4) treatment. Short-term exposure to a clinically effective MgSO(4) concentration in vitro substantially reduced the frequency of neonatal monocytes producing TNF-α and IL-6 under constitutive and TLR-stimulated conditions, decreasing cytokine gene and protein expression, without influencing cell viability or phagocytic function. In summary, MgSO(4) reduced cytokine production in intrapartum women, term and preterm neonates, demonstrating effectiveness in those at risk for inflammation-associated adverse perinatal outcomes. By probing the mechanism of decreased cytokine production, they found that the immunomodulatory effect was mediated by magnesium and not the sulfate moiety, and it was reversible. Cellular magnesium content increased rapidly upon MgSO(4) exposure, and reduced cytokine production occurred following stimulation with different TLR ligands as well as when magnesium was added after TLR stimulation, strongly suggesting that magnesium acts intracellularly. Magnesium increased basal I Bα levels, and upon TLR stimulation was associated with reduced NF-κB activation and nuclear localization. These findings establish a new paradigm for innate immunoregulation, whereby magnesium plays a critical regulatory role in NF-κB activation, cytokine production, and disease pathogenesis.