

Labyrinthitis, Vestibular Neuritis and Sensorineural Hearing Loss (SNHL)



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Abstract

This mini-review discusses pathogenesis and pathophysiology of vestibular neuritis, labyrinthitis and sensorineural hearing loss (SNHL). In addition, the role of the immune system as a therapeutic target in the treatment and course of these disorders is evaluated. Viral, bacterial, traumatic, congenitally acquired and hereditary causes are discussed. Results of the therapeutic applications of glucocorticoid, immunosuppressives and the new biologics are considered. Active target delivery of genetically modified monocytes seems at present the most attractive option for the treatment of SNHL if the surface of the delivery vehicle can be decorated with a ligand that selectively interacts with the target receptors.

Introduction

Vestibular neuritis and labyrinthitis are sometimes used interchangeably but “vestibular neuritis” should be confined to cases in which the vestibular nerve only is involved and the term “labyrinthitis” being used in cases in which the vestibular nerve and the labyrinth are affected. Vestibular neuritis is a very common cause of vertigo, labyrinthitis less so. Typically they produce disturbances of balance to varying degrees and may affect one or both ears. Essentially there is a sudden disruption of afferent neural input resulting in acute vertigo plus in the case of labyrinthitis, hearing loss [1].

Bacteria or viruses can cause acute inflammation of the labyrinth in conjunction with either local or systemic infections. Autoimmune processes may also cause labyrinthitis. Vascular ischemia may result in acute labyrinthine dysfunction that mimic labyrinthitis. Several mechanisms have been postulated as the pathophysiology of sudden deafness, including microthrombosis, microtrauma or rupture of endolymph, viral infection, bacterial infection and immune mediated reaction.

In this mini-review, the pathogenesis, pathophysiology of these disorders are discussed. In addition, the immune system as a therapeutic target and the treatment and course of vestibular neuritis, labyrinthitis and sensorineural hearing loss (SNHL) will be evaluated.

Pathogenesis of peripheral vestibulopathy (PVP)

Viral causes: PVP is often preceded by a viral infection of the upper respiratory tract [5]. Herpes viruses in the eighth and other cranial nerves were found as well in the saliva of patients [6-10]. Histopathological changes due to herpes viruses have been found in both the vestibular nerve and labyrinth [11]. HSV-1 has also

been detected in the labyrinth [6]. The anatomical evidence of a vestibulo-facial nerve anastomosis is one way of explaining those viruses in neurons [12]. However, the prevalence as described in those studies is insufficient to support herpes viruses as the only etiological factor. More likely, those findings point to the fact that PVP may have a multifactorial origin.

Often the case for the neuritis hypothesis (NH) is made by presenting PVP as analogous to Bell's palsy, which is also thought to be caused by a reactivation of viruses that subsequently leads to nerve edema and loss of function [6,13]. However, how reasonable this may seem there are two differences. Firstly, corticosteroids have been found to be reasonably effective in the treatment of Bell's palsy [14] while their effect in treating PVP is less established [15,16]. Other equally plausible agents should also be taken in account. For instance, herpes labialis, in which the reactivation of viruses, often proposed as a possible pathogenetic mechanism in PVP, leads to pathological changes in the skin. This would support a model with intralabyrinthine changes rather than an isolated neuritis.

Other evidence cited in favour of the NH includes MRI studies and histopathologic analyses. One MRI double case report mentions changes in the vestibular nerve but not in the labyrinth in two patients 7 and 11 days after symptom onset [17]. This study contradicts two others that looked at MRI's of 8 and 60 patients with PVP and found no signs of a neuritis [18,19]. Histopathological studies have found that there was evidence of viral infections and subsequent loss of neurons in the vestibular nerve. However, they also found significant changes in the labyrinth. There was “epithelization” on the otolith organs. This occurred in the maculae and the cristae of the SCCs (semicircular

canals) [20]. An animal study confirms the evidence of a viral infection of both the vestibular nerve and labyrinth [11].

The fact that benign paroxysmal positional vertigo (BPPV) is more prevalent in patients with a history of PVP also supports a pathogenetic model with involvement of an intralabyrinthine lesion [3]. As a whole these findings do not strongly support the neuritis hypothesis. It would therefore at least be prudent to consider the involvement of the vestibular labyrinth in the pathogenesis of peripheral vestibulopathy.

Bacterial causes: The advent of antibiotics and immunizations in the last century led to a considerable decline in the incidence of complications from otitis media and therefore a discussion on suppurative labyrinthitis with middle ear infection may seem, at first glance, an outdated issue. However, complications still occur, particularly in developing countries with significant morbidity resulting in hearing loss [21-26].

The diagnosis of suppurative labyrinthitis secondary to otitis media is essentially a clinical one through the observation of vertigo, nystagmus, tinnitus and hearing impairment in the presence of middle ear infection. In serous labyrinthitis symptoms are more subtle and many patients experience a satisfactory recovery with the treatment of underlying disorders of the middle ear. Little is known about the mechanisms involved in diseases of the human ear in vivo [27].

Imaging tests are important tools in an attempt to better understand the dynamics of inner ear inflammation. Currently the high-resolution computed tomography (HR-CT) best evaluates diseases affecting the inner ear and retrocochlear pathways. Recent advances in NMR technique offer interesting opportunities for the study of cochlear structure, function and metabolism in vivo. The use of gadolinium as a contrast for the study of the inner ear adds sensitivity to the NMR, particularly for diseases such as labyrinthitis [27-30].

Complications are labyrinthine fistula, meningitis, facial paralysis, mastoiditis, cerebral and temporal abscesses [31]. It is known that the sequence of events following an episode of suppurative labyrinthitis typically occurs in three stages. In the acute phase, bacteria and leukocytes appear in the perilymphatic space. In the fibrous phase, granulation tissue consisting of fibroblasts associated with neovascularization results in fibrosis. Finally the ossification phase is characterized by metaplastic bone formation [32]. In the radiological literature three phases of labyrinthitis are usually described as the acute, the fibrous stage and a Labyrinthitis ossificans, This division is however artificially and concomitant occurrence of these phases is possible [33,34].

Mofatteh et al. assessed the frequency of bacterial agents in chronic suppurative otitis media and the antibiotic susceptibility patterns of isolates among patients (n=185). *Staphylococcus* spp. (64,9%) were the most prevalent bacteria isolated, followed by *Klebsiella* spp. (12,9%) and *Pseudomonas aeruginosa* (10,3%).

The most effective antibiotic for treatment of bacterial chronic suppurative otitis media was ciprofloxacin. Statistical analysis showed no significant differences in bacterial infestations among chronic suppurative otitis media patients and the antimicrobial susceptibility patterns of the bacterial isolates based on gender and age ($p > 0,05$) [35].

Recently, the draft protocol for a Cochrane review of the role of probiotics for preventing acute otitis media in children was released [36].

Pathogenesis SNHL

In developed countries approximately 80% of congenital hearing loss is due to genetic causes and the remainder to environmental. Acquired causes should be differentiated from genetic causes for the evaluation and required ancillary testing (i.e., CT, MRI and consultation with specialists) and to inform prognosis and treatment recommendations.

Acquired hearing loss in children commonly results from prenatal infections from "TORCH" organisms (i.e., toxoplasmosis, rubella, cytomegalovirus and herpes) or post-natal infections, particularly bacterial meningitis caused by *Neisseria meningitidis*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*. Meningitis from many other organisms including *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus agalactiae* and *Enterobacter cloaca* can also cause hearing loss. In developed countries, however the most common environmental, non-genetic cause of congenital hearing loss is congenital cytomegalovirus (cCMV) infection. Its overall birth prevalence is approximately 0,64%. Ten percent of this number have symptomatic CMV, which is characterized by a variable number and degree of findings including neurologic deficits (death, seizures, cerebral palsy), hepatic insufficiency and characteristic rash. Hearing loss affects approximately 50% of symptomatic individuals with cCMV. The remaining 90% of individuals with cCMV are considered "asymptomatic". Of these up to 15% develop unilateral or bilateral hearing loss. Thus, the majority of individuals with hearing loss due to cCMV are classified as "asymptomatic" [37].

The diagnosis of CMV hearing loss can be difficult to make, often can go unrecognized and is characterized by variable-severity bilateral asymmetric or unilateral sensorineural hearing loss [38]. Testing for cCMV requires a high degree of suspicion and should be done within 21 days of birth given the ubiquity of the virus in the environment. Recognizing cCMV hearing loss is increasingly important given new studies that show improvement of hearing loss with antiviral therapy for persons with symptomatic CMV [39]. To date, the use of antivirals to treat hearing loss in persons with cCMV whose only manifestation is hearing loss is experimental.

Acquired hearing loss in adults is most often attributed to environmental-genetic interactions the most frequent of which are age-related and noise-induced hearing loss. Although both of these types of hearing loss reflect complex "environmental-genetic" hearing loss, to date variants in only a few genes have

been associated with these traits [40].

Approximately 80% of prelingual deafness is genetic, most often autosomal recessive. The most common cause of severe-to-profound autosomal recessive hearing loss in most populations is a mutation of GJB2. The most common cause of mild-to-moderate autosomal recessive hearing loss is a mutation of STRC [41].

Autoimmunity and SNHL

Immune-mediated inner ear disease has been introduced and accepted as a cause of SNHL. It responds to immunosuppressive therapy and is one of the reversible forms of bilateral SNHL. The concept of immune-mediated inner ear disease is straightforward and comprehensible but criteria for clinical diagnosis and the precise mechanism of hearing loss have not been determined. Moreover, the therapeutic mechanisms of corticosteroids are unclear [42].

Sensorineural hearing loss (SNHL) is a collection of common auditory disorders resulting from dysfunction of the inner ear, auditory nerve or the auditory processing pathway in the central nervous system. SNHL comprises a wide variety of auditory disorders including sudden deafness, age-related hearing loss, noise induced hearing loss and Meniere's disease. Until now very little of the pathophysiology is known because biopsy of the inner ear is not feasible. The cochlea has no lymphatic drainage and the blood-labyrinth barrier is tightly controlled to separate the cochlear microenvironment from the circulation. In addition, the concentration of immunoglobulin in the cochlear fluid is 1/1000 of the concentration in the cerebrospinal fluid [43]. McCabe introduced the clinical definition of autoimmune inner ear disease as rapidly progressive bilateral hearing loss that responds to corticosteroid and immunosuppressive therapy [4]. Steroid-responsive hearing loss does not always indicate an underlying inflammation or immune disorder in the inner ear [44]. Topical application of corticosteroids in the tympanic cavity have also been reported in patients unable to tolerate systemic treatment [45,46].

The pathophysiology of organ-specific autoimmune disease is believed to be initiated by three primary mechanisms:

- a) Production of autoantibodies against tissue antigens
- b) Deposition of antigen-antibody complexes in tissues
- c) Infiltration and destruction of tissue by specific cytotoxic T-cells.

The mechanisms of hearing loss in immune-mediated inner ear disease has yet to be determined and none of the three described mechanisms have been reported in the human inner ear. Immune-mediated SNHL progresses to deafness over weeks or months, not hours, days or years. The time course of hearing loss distinguishes immune mediated inner ear disease from sudden deafness or age-related hearing loss. There are

no uniformly accepted criteria of immune-mediated inner ear disease. The presence of bilateral SNHL of at least 30dB with evidence of progression in at least one ear or two serial audiograms performed less than 3 months apart is often used as case criteria [47]. Fluctuations in hearing loss may occur and immune-mediated disease is one of the few reversible causes of SNHL.

Multisystemic organ-nonspecific autoimmune pathology may involve the inner ear leading to secondary SNHL. A limited number of studies have evaluated temporal bones from patients with autoimmune disease such as Wegener granulomatosis, polyarteriitis nodosa, Cogan syndrome and lupus [47,48]. Some specimens showed fibrosis and osteogenesis consistent with the end stage of inflammation. Other bones demonstrated atrophy of the stria vascularis, the organ of Corti and the spiral ganglion without evidence of inflammation. Dettmer et al. reported that the temporal bones of Crohn's disease patients with granulomatous ear disease demonstrated mild chronic inflammation, poorly defined granulomas and infiltration of CD68-positive macrophages [49].

The first evidence for involvement of the immune system in SNHL was supported by studies of Rusk-Andersen and Stahle. They showed intimate contact between lymphocytes and macrophages in the endolymphatic sac of guinea pigs [50]. This association suggested that two cell types mediated the antigen presenting process in the endolymphatic sac. The presence of immunocompetent cells and phagocytized antigen within macrophages was also reported in the endolymphatic sac [51].

However, recent studies have demonstrated the presence of immunoreactive cells in other areas of the inner ear even under normal conditions [52-54]. Lang et al. [52] reported that bone marrow-derived cells of hematopoietic origin migrate into the cochlea and reside in the cochlear modiolus and the cochlear lateral wall. They also showed that bone-marrow derived cells in the cochlea express ion transporters such as the sodium-potassium-chloride cotransporter or sodium-potassium-ATPase in the cochlear lateral wall, which contains several types of fibrocytes. In a study using bone marrow-chimeric mice that were transplanted with hematopoietic stem cells after receiving lethal systemic irradiation Okano et al. demonstrated that bone marrow derived cells reside as macrophages in the cochlea. They also reported that Iba-1 positive macrophages were continuously and slowly replaced by bone-marrow derived cells from the systemic circulation over several months [53]. Finally, Sato et al. reported that bone marrow-derived cells expressing CX3CR1, a fractalkine receptor specific to monocytes, natural killer cells, activated T-cells and tissue macrophages reside in the spiral ganglion and spiral ligament. In addition, they showed that CX3CR1-positive cells were repopulated in the cochlea over several months [54]. Collectively these findings indicate that the inner ear harbors immunocompetent cells of hematopoietic origin, which most cells likely to be tissue macrophages phenotypically.

The role of cochlear macrophages and mechanisms of macrophage migration into the cochlea remain largely unknown. The number of cochlear macrophages is also increased by systemic administration of macrophage colony stimulating factor (CSF-1) which is one of the primary regulators of mononuclear phagocyte activation. The density of Iba1-positive macrophages is increased in both the spiral ligament and spiral ganglion 1 day after administering CSF-1 but it is unclear whether the increased macrophage population is due to migration from the circulation or in situ proliferation in the cochlea [54]. Yagihashi et al. also demonstrated that topical administration of CSF-1 ameliorates the degradation of auditory neurons following surgical injury in a rat model [55]. In addition, CSF-1 was demonstrated to have neuroprotective properties in an in vitro model of excitotoxicity in hippocampal neurons, suggesting both direct and indirect effects of CSF-1 on survival of targeted cells [56].

Previous reports investigating in situ proliferation of cochlear macrophages are controversial. Using bromodeoxyuridine labeling Hirose et al. reported that cochlear macrophages do not proliferate after acoustic trauma [57]. However, according to the study done by Okano et al. a subset of macrophages expressed Ki67, suggesting that resident macrophages enter the cell cycle after migration following surgery of the cochlea [54]. Although the precise nature of migrating macrophages is to be determined, cochlear macrophages are most likely responsible for several different inner ear pathologies.

Macrophages are derived from monocyte precursors that undergo tissue-specific differentiation and infiltrate the site of infection or injury to produce inflammatory mediators. The cells typically polarize into the pro-inflammatory M1 phenotype and function as an effector of the Th-1 mediated immune response. The M1 polarization of macrophages is regulated by several factors including the mineralocorticoid receptor [58]. In the normal course of inflammation the immune process is controlled. M1 macrophages undergo apoptosis or switch to the anti-inflammatory M-2 phenotype thereby halting inflammation. However, if the inflammatory response of macrophages is not controlled it becomes pathogenic. This results in significant levels of non-specific tissue damage and leading to inflammatory and autoimmune diseases [59]. Therefore, macrophage-targeted therapy is extremely relevant in improving the prognosis of inflammatory diseases, particularly inflammation in the inner ear.

Thought provoking observations have been made in studies of patients with human immunodeficiency virus (HIV) concerning macrophage function in the inner ear. Monocytes and macrophages are susceptible to HIV-infection and are considered a main mechanism responsible for control of nervous system infection in areas containing perivascular macrophages and parenchymal microglia [60]. Lin et al. [61] demonstrated that HIV infection is significantly associated with an increased risk of developing sudden deafness in patients aged between 18 and 35 years. In addition, Assuiti et al. found no direct association

between anti-retroviral therapy and hearing loss [62]. These data suggest that deficiencies in the macrophage and monocyte lineage may lead to dysfunction in the inner ear and highlight the important role of macrophages in the maintenance of auditory function.

Several surface markers have been used in animal studies of macrophages to immunohistochemically test their phenotypes and distribution in the tissues. CD68 is a heavily glycosylated transmembrane protein and is a common surface marker expressed in all macrophages [63,64]. F4/80 is a member of a gene family that includes the human epidermal growth factor module-containing mucin-like hormone receptor1 and human CD97. They reside on the surface of a family of cells that includes all well differentiated members of the mononuclear phagocyte system. The precise function of F4/80 is not completely understood as F4/80 null mice have no remarkable phenotype. They have many common features regardless of their tissue location and are characterized by highly ramified cell shape [65]. Iba1 is a calcium binding protein specific to macrophages that mediates calcium signals that may control migration and phagocytosis in tissue macrophages [66]. Tissue macrophages in the inner ear express Iba1 in addition to F4/80 [54]. Csf1r is an alternative surface marker on macrophages and is thought to play key roles in the proliferation, differentiation and survival of macrophages [65]. In other categorical systems, the differentiation of monocytes and macrophages is described as the expression of specific cell markers. If similar markers could be identified in tissue macrophages or cells of monocyte lineage it may be possible to trace these cells along several different points of the inner ear pathophysiology, including systemic circulating monocytes, migrating monocytes and resident tissue macrophages.

Systemic or possible local administration of corticosteroids is the mainstay of treatment for SNHL, including immune-related inner ear disease. There are limited prospective data evaluating the appropriate dose, route and length of corticosteroid treatment. Although many patients experience a short-term response to steroids this response is generally not sustained [67]. A prospective, randomized, controlled study in 116 patients with rapidly progressive bilateral SNHL reported that 57% of patients in the 1 month prednisone challenge showed improved hearing but adverse effects as hyperglycemia were observed in 14% of patients [68]. A meta-analysis of the management of idiopathic sudden SNHL by Spear and Schwartz reported that intratympanic corticosteroids administered as the primary treatment appeared equivalent to treatment with high-dose oral prednisone [69]. Furthermore, intratympanic administration of corticosteroids potentially recovered some degree of hearing as a salvage therapy. These observations suggest that the local administration of corticosteroids is beneficial from that of systemic corticosteroid therapy.

Despite numerous clinical reports of corticosteroid treatment for SNHL, the spontaneous rate of recovery in acute

SNHL complicates conclusions about corticosteroid efficacy. The expression of glucocorticoid receptors in the inner ear is limited to the inner and outer hair cells, the spiral ganglion and the spiral ligament [70,71]. In addition to glucocorticoid receptors corticosteroids have a strong affinity for mineralocorticoid receptors. The use of systemic mineralocorticoids alone or in combination with glucocorticoids has not been evaluated in humans but is apparently efficacious in animal models [72]. Because the inner ear requires tight regulation of ion homeostasis in both the perilymph and endolymph the effect of corticosteroid therapy through mineralocorticoid receptors should be considered in the mechanism of action when treating SNHL [4].

McCabe recommended high dose corticosteroids along with cyclophosphamide therapy for prolonged treatment of immune-mediated inner ear disease [4,48]. The extended follow-up of patients treated with cyclophosphamide revealed potential adverse effects and long-term morbidity and mortality risks of the agent, particularly neoplasm development in younger patients which limited its use. This prompted the search for other immunosuppressive therapies [51,73].

Methotrexate has been used as a sparing treatment to control refractory immune-mediated SNHL. Sally et al. reported improvement in the majority of 53 patients with immune-mediated inner ear diseases who were treated with low-dose methotrexate [74]. Long-term, low-dose methotrexate therapy appeared to be effective in at least some patients with immune-mediated hearing loss that is refractory to traditional corticosteroid therapy [75]. By contrast, a randomized, double blind, placebo-controlled trial of immune mediated inner ear disease suggested that methotrexate does not appear to be effective in maintaining the hearing improvement achieved with prednisone therapy [76]. Azathioprine was also reported as an alternative option in treating immune-mediated inner ear disease although reports were based on small case series and were inconclusive [77]. According to these findings immunosuppressives such as methotrexate are effective in some patients with bilateral progressive or fluctuating SNHL. However, patients with bilateral fluctuating SNHL do not always have an immune disorder in the inner ear.

Molecular-targeted drugs and biological agents have attracted attention due to their specificity against therapeutic targets resulting in less toxicity and fewer adverse effects. Etanercept is a fusion protein comprising two recombinant tumor necrosis factor (TNF) receptors linked to the C portion of human Ig1 [78]. A retrospective case series by Rahman et al. examined the response to etanercept in 12 patients with immune-mediated hearing loss responsive to high-doses of corticosteroids [79]. Improvement or stabilization of hearing and tinnitus was observed in 91% of patients suggesting that etanercept therapy is safe and may be efficacious in some patient's immune-mediated hearing loss. By contrast, two studies reported that etanercept has no substantial efficacy in improving hearing loss [80,81].

Infliximab is another monoclonal antibody against TNF-alpha that binds TNF-alpha and reduces its activity [82]. A retrospective review of eight patients with suspected immune-mediated hearing loss refractory to conventional treatment examined the efficacy of infliximab on hearing improvement. None of the patients showed a positive response to infliximab based on objective measurements [83]. Monoclonal antibody therapy directly targeting cells in the inner ear is unlikely to be effective because the concentration of immunoglobulin is much lower in this region than that in cerebrospinal fluid or blood due to the tight regulation by the blood-labyrinthine barrier. Accordingly, transympatric administration was evaluated by Van Wijk et al. in nine patients with immune-mediated hearing loss [84]. Transtympanic administration of infliximab resulted in hearing improvement and reduced relapses indicating the potential utility of local administration of monoclonal antibody in treating inner ear disease. Adalimumab was also used to block TNF signalling in patients with immune-mediated hearing loss but reports were based on a small number of cases [85].

Rituximab is a genetically engineered chimeric monoclonal antibody against CD20 which resides on the surface of B cells. The agent reduces autoantibody production both in circulating and tissue B cells but does not affect plasma cells. A small pilot study in patients with immune-mediated inner ear diseases was performed evaluating the efficacy of rituximab in treating hearing loss [86]. Further evaluation of rituximab is encouraged using a properly designed study.

Nucleic acid therapy, including delivery of gene constructs to increase or force expression in the targeted tissue and small interfering RNA to block expression of a specific gene, is a promising approach for treating inner ear disease. Limited access to the lesion site creates challenges in nucleic acid therapy of the inner ear. Various studies employing animal models utilize viral vectors to introduce the nucleic acid in the inner ear. There are toxicity and safety concerns associated with this method including immunogenicity and mutagenesis. Non-viral vectors are advantaged by overcoming these limitations including plaque viral vectors. Although nucleic acid therapy is challenging in the in vivo setting the development of novel delivery systems could lead to drastic advances in improving the prognosis of patients with SNHL. Obviously, macrophages are a potential target for nucleic acid therapy using novel delivery systems in the inner ear, controlling not only inflammation and degeneration of sensory organs but also regeneration of the cochlear lateral wall and innervation from the spiral ganglion neurons to hair cells.

The use of genetically modified monocytes or macrophages as vectors should be considered for production of therapeutic molecules or factors that promote regeneration or regrowth of specific structures in the inner ear. This concept is especially well suited for a secreted paracrine or endocrine factor such as a hormone or growth factor. Because the inner ear contains three fluid-filled compartments, secreted factors from genetically modified macrophages could potentially diffuse throughout the

inner ear without help from the blood or lymphatic circulation. Although the use of genetically modified cells as vectors of genes or pharmacotherapeutic agents is in the early stage, transplantation of genetically engineered cells able to secrete specific metabolic or humoral cues could augment pharmacologic immune modulation in the inner ear [87,89].

Delivery of genetically modified cells into the inner ear could pose a major challenge because of the anatomical characteristics of the inner ear. Monocytes and macrophages are able to migrate into the inner ear. In both pathologic and normal conditions [53,57]. Thus, the human monocyte lineage could be isolated and cultured *ex vivo* and genetically manipulated. Intravenous administration of genetically modified monocytes could enable them to reach and migrate into the inner ear, although tissue or organ specificity could be a potential problem to overcome in clinical applications.

Apart from resident macrophages at the disease site circulating monocytes are continuously recruited to meet the demands of the inflammatory response and the expression of chemokines, cytokines and cell adhesion molecules. An alternative approach is to facilitate phagocytosis of loaded delivery vehicles by monocytes which passively targets the site of disease due to the mounting immune response. The active targeting response is most attractive and promising if the surface of the delivery vehicle can be decorated with a ligand that selectively interacts with their target receptors. Further research evaluating the use of monocytes as vehicles is desired. Literature linking labyrinthitis, vestibular neuritis and SNHL to the gut-microbiome-brain axis is not available, yet.

Conclusion

Recent advances in basic and clinical audiology and immunology research have been rapid. Particularly, the role of the innate immune system and the pathology of immune-mediated related inner ear disease is more evident now. Passive and preferably active target delivery of genetically modified monocytes is at present the most attractive option for the treatment of SNHL if the delivery vehicle can be decorated with a ligand that interacts with the target receptors. So, the future of the treatment of SNHL looks bright.

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