Turkish Journal of Immunology - Open Access
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Turk J Immunol 2019; 7(1):S92–S98

Immune-mediated Sensorineural Hearing Loss: Patho-Mechanisms and Therapeutic Strategies

İmmün Aracılı Sensorinöral İşitme Kaybı: Patolojik Mekanizmalar ve Terapötik Stratejiler

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Abstract

The immune system protects the inner ear from various infections. However, the fragile audiological and vestibular structures are damaged due to immune-related and inflammatory responses, thus resulting in sensorineural hearing loss. Immune-mediated sensorineural hearing loss (ISNHL) can either be of autoimmune or autoinflammatory origin, and studies have shown that ISNHL ultimately results from inflammatory responses in both the cases. Several disorders have been identified that either primarily cause hearing loss due to localized inflammation (such as Meniere's disease) or as an additional manifestation resulting from systemic inflammation (as seen in Muckle-Well syndrome). Immune molecular- and patho-mechanisms have been proposed to explain ISNHL, yet it has been an enigma. A crucial mechanism leading to immune activation and inflammation involves the increased levels of NLRP3 inflammasome-associated IL-1β and TNF-α, in resident macrophages of the inner ear. The presence of autoantibodies to inner ear antigens have been reported as a causative ISNHL and these antibodies also serve as diagnostic markers. Genetic-susceptibility to ISNHL in some individuals has been reported. ISNHL is reversible, where hearing and vestibular functions can be restored. Several studies have put forward therapeutic strategies to alleviate hearing impairment, by usage of immunosuppressive drugs, monoclonal antibodies, IL-1β and TNF-α antagonists, and NLRP3 inflammasome-inhibitors. Emerging approaches for treating autoimmune disease include altering gut microbiota, stem cell therapy and precision medicine. The present report reviews the various molecular- and patho-mechanisms associated with ISNHL. It further focuses on possible therapeutic targets and the relevance in application of emerging therapeutic strategies to alleviate hearing loss.

Keywords: Immune-mediated hearing loss, ISNHL, inflammasome, IL-1β, NLRP3, TNF-α

Öz

Bağışıklık sistemi, iç kulağı bir dizi enfeksiyondan korur. Bunun ile birlikte, duyusal ya da vestibuler yapılar, bağışık kökenli ya da enflamatuvar yanıtlar ile sensörinöral işitme kaybına neden olacak şekilde hasar görebilir. Bağışıklık sisteminin neden olduğu sensörünöral işitme kaybı (BNSNİK) otoimmün ya da otoenflamatuvar nedenli olabilir. Çalışmalar, BNSNİK'nın her iki durumda da enflamatuvar kökenli olduğunu göstermektedir. İşitme kaybına neden olan durumlar, Menier hastalığında olduğu gibi lokalize enflamasyon ile de olabileceği gibi, Muckle-Well sendromundaki gibi sistemik enflamasyona da bağlı olabilir. SNİK'na neden olan moleküler ve patolojik mekanizmalar henüz bilinmemektedir. Bu duruma neden olan bağışıklık aktivasyonu ve enflamasyon, iç kulakta bulunan makrofajlardan NLRP3 inflamazomuna bağlı olarak salınan IL-1β ve TNF-α'dır. SNİK, iç kulaktaki antijenlere karşı oluşan antikorlara bağlı olarak oluşmaktadır ve bu antikorlar aynı zamanda hastalığın tanısında da kullanılabilir. Bazı kişilerde, SNİK'ya karşı kalıtsal bir yatkınlık olduğu bildirilmiştir. SNİK'da duyma ve denge işlevleri geri dönebilir. Duyma bozukluğunu tedavi etmek için bağışıklığı baskılayıcı ilaçlar, monoklonal antikorlar, IL-1β, TNF-α antagonistleri ve NLRP3 inflamazom inhibitörleri gibi ajanların kullanıldığı bazı çalışmalar yapılmıştır. Bunlar dışında, barsağın mikrobiatasını değiştirmek, kök hücre tedavisi ve hedefe yönelik tedaviler gibi yeni yöntemler de gündeme gelmektedir. Bu yazıda, SNİK'ya neden olan farklı moleküler ve patolojik mekanizmaların bir derlemesi sunulmaktadır. Bu yazı, aynı zamanda işitme kaybının tedavisi için, ileride yönelenebilecek hedefleri ve yeni tedavi stratejilerini de işaret etmektedir.

Anahtar Kelimeler: Bağışıklık nedenli işitme kaybı, ISNHL, inflamazom; IL-1β, NLRP3, TNF-α

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Received: Jan 07, 2019
Accepted: Feb 18, 2019

https://doi.org/10.25002/tji.2019.1015

Introduction

The sound signals are converted to electric impulses by the mechano-sensory hair cells of the inner ear; these impulses are transmitted by the eighth cranial nerve that starts as the spiral ganglia in the inner ear. The inner ear hair cells lack the capacity to regenerate, therefore, damage or death of these cells results in permanent hearing loss. The immune

system protects against infectious agents. Previously, the inner ear was regarded as an immune-privileged site, due to the presence of the blood-labyrinth barrier.[1] However, later studies showed infiltration of lymphocytes in the inner ear. Initially, the immune responses involving lymphocyte infiltration and inflammation, resulting in cochlear damage was observed when a systemically sensitized antigen was introduced into the inner ear.[2] The endolymphatic sac harbors lymphocytes that play a crucial role in immune responses in the ear.[3] Immune responses in the inner ear can be described as a 'double-edged sword' , where, deregulation or tampering of the immune responses can damage the fragile auditory and vestibular structures, resulting in hearing loss (HL).[4] Immune responses in the ear can cause both sensorineural and conductive hearing loss. This review focuses on immune-mediated sensorineural hearing loss (ISNHL), as it is more prevalent than conductive hearing loss.

Immune-mediated sensorineural hearing loss (ISNHL) is defined as progressive sensorineural hearing loss which responds to treatment with immunosuppressive agents; sometimes the onset of HL can be sudden (sudden SNHL).[5] It is one of the few forms of reversible HL, and when diagnosed properly, it has scope for various management and therapeutic strategies; recovery of sustained profound SNHL is highly unlikely.[4] Even after extensive research, diagnosis of ISNHL and its causative patho-mechanisms are enigmatic. This review deals with the various patho-mechanisms that explain the occurrence of ISNHL, highlighting the application of traditional and prospective therapeutic strategies in treating and alleviating ISNHL.

ISNHL in autoimmune and autoinflammatory diseases

ISNHL constitutes >1% of all hearing loss cases; due to the absence of specific diagnostic tests and complexity of differential diagnosis, the prevalence of ISNHL is usually underestimated.[6] ISNHL can result from autoimmune or autoinflammatory disorders, both of which ultimately damage the inner ear by inflammatory responses. Autoimmune diseases are caused due to the deregulation of adaptive immune system, driven by autoreactive antibodies of B-and T-cells; while autoinflammatory diseases such as Muckle-Wells syndrome and NOMID, result from abnormal innate immune system that are characterized by acute inflammatory episodes. Autoimmune diseases can be (i) systemic (affects multiple organ systems) as in systemic lupus erythematosus (SLE), Sjogren's syndrome and multiple sclerosis and sarcoidosis, or localized (targets specific organs/tissues-inner ear, here) as in Meniere's disease, Cogan's syndrome and cochlear vasculitis.[7] However, even with the vast phenotypic heterogeneity among autoimmune and autoinflammatory diseases, the underlying causative can be overlapping.[8]

Sensorineural hearing loss (SNHL) is the most prominent audiological feature in several systemic autoimmune diseases.[9] About 15–30% of systemic autoimmune disease have SNHL as a clinical manifestation.[6] The prevalence of SNHL and the phenotypes are highly variable among the different diseases and between individuals with the same disease. SNHL has been reported in autoimmune diseases with a frequency as high as 80–90% and only in isolated cases in some diseases; however, the exact prevalence of ISNHL in these disorders is still unknown (reviewed by Ralli, et al.[10]). Immune responses localized to the inner ear cause diseases in which HL is the primary clinical manifestation, such as autoimmune inner ear disease, Meniere's disease, otosclerosis, cochlear vasculitis and sudden hearing loss.[6,7]

Immune responses and mechanism of ISNHL

The inner ear is known to mount immune-responses that can damage the cochlea and spiral ganglion, resulting in SNHL.[4] Several studies have been carried out to understand the possible mechanisms underlying the immune-responses leading to inner ear damage. The endolymphatic sac is crucial for immune-modulation in the inner ear.[11] In the presence of an antigen, the cochlear innate immunity initiates the adaptive response and the lymphocytes from systemic circulation pass through the blood-labyrinth barrier to reach the endolymphatic sac.[11] The macrophages and granulocytes (innate immune cells) of the inner ear are primarily found in the endolymphatic sac, scala vestibuli and scala tympani; while the adaptive immune cells B and T lymphocytes are present in the systemic circulation, they infiltrate the scala vestibuli, scala tympani and endolymphatic sac upon induction.[12,13] Scala tympani has been proposed as the site of initial entry of the lymphocytes.[12,13]

The pathophysiology of ISNHL is not clearly known, however, autoantibody (against inner ear antigens) driven cell-mediated cytotoxicity, complement activation

Turk J Immunol 2019; 7(Supplement 1):S92–S98

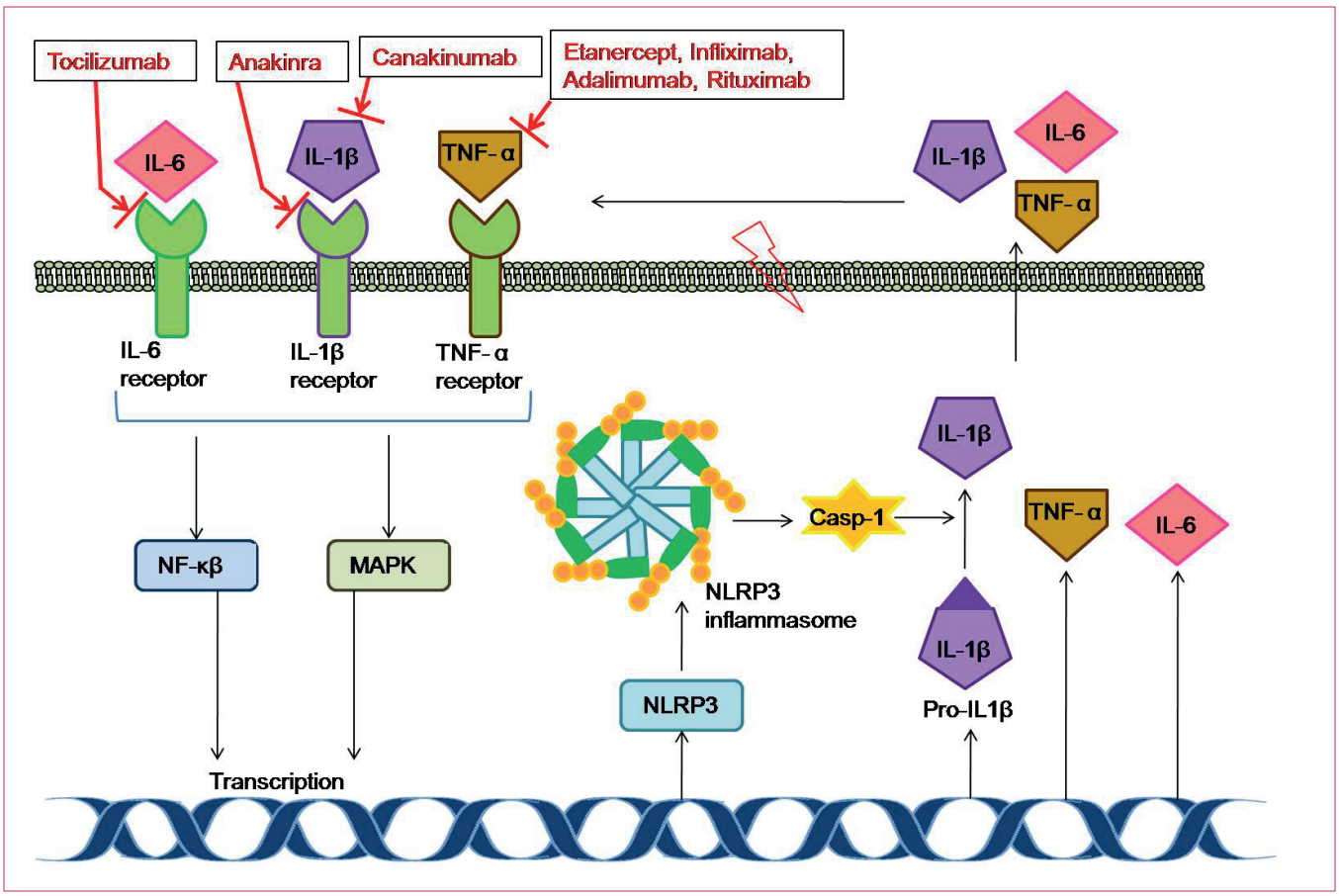

Figure 1. Therapeutic agents targeting the cytokines that play an important role in autoimmune and autoinflammatory diseases.

and immune-complex deposition, have been proposed as possible mechanisms.[10] Chronic activation of self-reactive helper T-cells play a role in damaging the cochlear sensory hair cells and supporting cells. Deposition of immune-complexes in the labyrinthine artery has been proposed as a crucial factor in immune-mediated SNHL. The deposition of immune-complexes leads to vasculitis (inflammation and thickening of blood vessels), resulting in reduced oxygen supply (hypoxia) in the inner ear. Hypoxia increases generation of reactive-oxygen species, which in turn damages the hair cells and spiral ganglion.[14] Sudden SNHL has been reported to result due to temporary reduction of blood flow in the inner ear (vasculitis), where partial or complete recovery is possible after restoration of blood flow; persistent vasculitis is known to permanently damage hearing.[15]

The cytokines that play a crucial role in ISNHL are TNF-α, IL-1β, and IL-6;[16-20] NLRP3 inflammasome-mediated upregulation of IL-1β plays an important role in immune-mediated damage (Figure 1). Recognition of antigens by innate immune cells induces the release of IL-1β, which in turn prompts adaptive immune response.[21] Autoantibodies targeting inner ear antigens cause autoimmune-related damages to the hair cells, supporting cells and the spiral ganglia of the inner ear.[22] In the presence of an inflammation due to infection, antibody cross reactivity, ROS, etc), the TNF-α is produced by the spiral ligament fibrocytes, outer hair cells, and supporting cells within the organ of Corti, regulates cell death via NF-κβ and MAPK.[23] Simultaneous production of IL-1β and TNF-α can escalate inflammation and damages the inner era.[22]

Autoantibodies against self-molecules have been reported to play crucial roles in autoimmune and autoinflammatory diseases. Anti-DNA autoantibodies that were proposed to induce apoptosis in inner ear hair cells and spiral ganglion were observed in SLE patients.[24] Autoantibodies against Cogan peptide has been observed in patients with Cogan's syndrome; Since the Cogan peptide shares sequence similarity with Connexin-26

and CD-148 (expressed in the inner ear), it has been proposed that these autoantibodies play a role in causing the ISNHL phenotype.[24] Autoantibodies specific to Hsp-70, type II collagen, type IX collagen, Raf-1, myelin protein P0, β-actin, CTL2, β-Tectorin and KHRI-3 have been identified in autoimmune diseases. These antigens are found in critical regions of the inner ear such as the hair cells, spiral ligament, labyrinth, basilar membrane, endolymphatic sac and supporting cells.[22] Infiltration of autoantibodies against these antigens into the inner ear can be detrimental.

Other than these inner ear-specific autoantibodies, the presence of tissue non-specific autoantibodies such as anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (against myeloperoxidase (c-ANCA) and proteinase-3 (p-ANCA)), anti-endothelial cell antibody (AECA), anti-phospholipid/anti-cardiolipin antibodies, anti-thyroid antibodies, Rheumatoid factor and HSP-70 antibodies are proposed as diagnostic markers.[25–27]

Genetic susceptibility to ISNHL

Genetics and environmental factors are known to play a major role in the pathogenesis of autoimmune and autoinflammatory diseases.[28] A few genetic variants associated with autoimmune and autoinflammatory disease have been reported to confer predisposition to development of ISNHL. Mutations affecting the various inflammasome-related genes have been reported in autoinflammatory diseases.[29] The NLRP3 gene encodes cryoporin, which is a key component of the NLRP3 inflammasome.[30] Upon activation, the NLRP3 inflammasome initiates ASC-mediated activation of caspase-1, which in-turn cleaves pro-IL-1β to synthesis mature IL-1β.[30] Gain-of-function mutations in the NLRP3 gene causesCAPS (Cryoporin-associated periodic syndromes), which is an autosomal dominantly inherited systemic autoinflammatory disease spectrum (including Muckle-Wells syndrome, NOMID and FCAS)[31–33]; somatic mosaicism of NLRP3 were also reported in NOMID cases.[34] These mutations probably affect negative regulation of the NLRP3 inflammasome and thus resulting in over-production of IL-1β. A missense mutation in the NLRP3 gene was reported to cause autosomal dominant non-syndromic hearing loss-DFNA84 (milder severity).[35]

The gene NLRP12 encodes a pyrin domain-containing protein, NALP12.[36] NLRP3 mutation negative patients who showed disease manifestations characteristic of CAPS (with SNHL) were reported to have mutations in the NLRP12.[37] Previously mutations in the gene are known to cause Wolframin syndrome 1 (characterized by diabetes mellitus, optic atrophy, SNHL and psychiatric disorders). Hildebrand et al (2008) reported WFS1 gene mutations segregating with autoimmune diseases (Graves disease & Crohn's disease) in two hearing impaired individuals from a family.[38] A longitudinal study in the Japanese population reported polymorphisms in the genes TNF-α and TNFRSF1B that imposed a significant risk in developing hearing loss.[39]

Therapeutic strategies for ISNHL

The traditional and common treatment for ISNHL is corticosteroid therapy, which has been employed for more than 60 years.[3,40] Steroids such as prednisone, prednisolone, methylprednisolone and dexamethasone are used predominantly.[40] The widely used recommendations for corticosteroid treatment include an initial treatment with 60 mg/day prednisone for 4 weeks that is further continued until the hearing stabilizes. Then, the dosage is tapered to 10 mg over a period of 8 weeks.[41] In case of relapses, treatment with dosage escalation over a period of 6 months is given until hearing stabilizes. Corticosteroids have been used in systemic therapy and adverse effects occur in about 15% of the cases; for these individuals intratympanic route of administration is done. However, a study on 11 patients reported intratympanic administration of 6-methylprednisolone over a period of 2 months, improved hearing.[42] When the disease is non-responsive non-steroidal immunosuppressants like methotrexate and cyclophosphamide are used, either individually or in combination with corticosteroids to enhance the alleviatory effects.[1] However, these agents have been associated with adverse effects such as liver, bone-marrow, gonadal, bladder and gastrointestinal toxicities.[25] Plasmapheresis has also been done; it was reported to improve hearing in 50% of the patients.[44]

Therapeutic agents such as monoclonal antibodies and antagonists have been designed to modulate various components of the inflammatory cascade. TNF-α targeting monoclonal antibodies such as etanercept[45], infliximab[46] and adalimumab[47] have been used in patients to treat ISNHL. A chimeric monoclonal antibody called Rituximab, targeting the B-cell CD20 receptor and TNF-α has been reported to show progressive results.[48]

Tocilizumab is a humanized monoclonal antibody that targets the IL-6 receptor; it has been used to treat a case of Cogan's syndrome.[49] Anakinra is a recombinant IL-1β receptor antagonist; that found to be effective in a small cohort of patients with corticosteroid-resistant ISNHL[50]; randomized controlled studies would be helpful to conclusively state its efficacy. Yet another monoclonal antibody, Canakinumab, is an IL-1β blocker, which was found to have a better efficacy than Anakinra, among patients with Muckle-Wells syndrome (Figure 1).[51] It was proposed to have an efficacy in alleviating the symptoms, however, this requires validation with a larger cohort.

Another therapeutic strategy for ISNHL is cochlear implantation, which has been reported to be a safe and viable option when steroid treatment is not suitable; nevertheless, the decision for cochlear implantation should be made before the post-inflammatory obliterative changes set in.[52,53] Cochlear ossification and fibrosis was observed as a setback among approximately 50% of the patients undergoing cochlear implantation.[52,53]

Immuno-modulatory human adipose-derived mesenchymal stem cells (hAdMSC) have shown promising efficacy in treating immune-mediated manifestations in animal models; A study indicated an improvement of hearing in one patient.[27] Autologous AdMSCs have been suggested as a safe and efficient option for treatment of various autoimmune diseases and complications including ISNHL.[54]

Regeneration of hair cells and gene therapy have been studied as potential therapeutic strategies for hearing loss.[55,56]Hair cell regeneration involves trans-differentiation of the supporting cells into the mechano-sensory hair cells, by inhibiting the NOTCH pathway.[57] It is a promising strategy for individuals with non-genetic HL, such as noise-induced HL and ISNHL.[58]

Another interesting and futuristic therapeutic strategy is associated with the gut microbiome. The relationship between gut microbiome and immune-related diseases was thought to revolve around the regulation of immune-responses by the metabolites secreted by the microbiota.[59,60] Gut dysbiosis (altered gut microbial composition and diversity) has been reported in several immune-related diseases such as inflammatory bowel disease, ulcerative colitis, multiple sclerosis, Graves disease, SLE.[61] Altering or modifying gut microbiota was studied as a possible therapeutic strategy for systemic immune-mediated diseases.[62,63]

Conclusions and future perspectives

Although there is phenotypic variability among immune-mediated diseases causing SNHL, the underlying mechanisms are expected to be similar. Several efforts are being made to understand the molecular mechanisms for devising therapeutic strategies. Being one of the very few forms of reversible HL, ISNHL has a lot of scope for development of therapeutic strategies. Apart from the traditional corticosteroid therapy, efficacy of monoclonal antibodies targeting the various cytokines of the immune responses are studied. In the age of pharmacogenomics, understanding the genotype and resulting phenotype would aid in effective precision medicine. Other than these, hair cell regeneration, gene therapy and stem cell therapy are upcoming therapeutic strategies that need refinement to achieve the desired results. Another exciting approach is understanding of the gut microbiome and its associated immune-responses, which could possibly transform into future therapies.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: Concept: PVS, KMR, CRS; Literature search: PVS; Writing manuscript: PVS; Critical Review: KMR, CRS.

Acknowledgements: CRS gratefully acknowledges support by the Ad-Hoc research project (5/8/10–17 (Oto)/CFP/2011-NCD-I) by Indian Council of Medical Research (ICMR); PVS is supported by ICMR-SRF (45/1/2016-HUM-BMS).

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