Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(7) 2865–2872
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DOI: 10.1177/0300060519847860
journals.sagepub.com/home/imr
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Role of viral infection in sudden hearing loss

Xin Chen[1,*], Yao-yao Fu[1,*] and Tian-yu Zhang[2]

Abstract

According to a recent epidemiological survey, the incidence of sudden sensorineural hearing loss (SSNHL) is increasing yearly. The cause of SSNHL is of great interest in research. To date, viral infection, vascular occlusion, abnormal cellular stress responses within the cochlea, and immune-mediated mechanisms are considered the most likely etiologies of this disease. Among these etiologies, the relationship between viral infection and sudden deafness has been unclear. In this review, we mainly discuss the viral hypothesis of SSNHL. There is little research proving or clearly indicating the pathogenesis of this disease. Further research is needed to elucidate the precise etiopathogenesis to better understand SSNHL and establish more suitable treatment to help restore hearing in affected patients.

Keywords

Sudden sensorineural hearing loss, viral infection, pathogenesis, etiology, otolaryngology, pathology

Date received: 7 November 2018; accepted: 10 April 2019

Introduction

Sudden sensorineural hearing loss (SSNHL) is an emergency of otolaryngology characterized by rapid onset of hearing loss or a progressive loss over 12 hours, with an average hearing loss of more than 30 dB on at least three contiguous frequencies within 72 hours. It has been reported that the incidence of SSNHL is 5 to 20 cases per 100,000 people per year.[1] However, a German study published in 2009 has

[1]ENT institute, Eye & ENT Hospital of Fudan University, Shanghai, China
[2]ENT institute, Eye & ENT Hospital of Fudan University, Shanghai, China; Hearing Medicine Key Laboratory, National Health and Family Planning Commission, Shanghai, China

*These authors contributed equally to this article.

Corresponding author:
Tian-yu Zhang, ENT institute, Eye and ENT Hospital of Fudan University, Shanghai 200031, China; Hearing Medicine Key Laboratory, National Health and Family Planning Commission, 83 Fenyang Road, Shanghai 200031, China.
Email: ty.zhang2006@aliyun.com

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estimated that there are 160 cases of SSNHL per 100,000 people annually.[2] Epidemiological surveys also show that the incidence of sudden deafness is increasing.[3,4] Because of the relatively low incidence of SSNHL, neither its etiology nor adequate therapy can be determined with certainty. The most commonly suspected etiologies of SSNHL include viral infection,[5] vascular occlusion,[6] abnormal cellular stress responses within the cochlea,[7] and immune-mediated mechanisms.[8] Many studies that have proposed a possible association between viral infection and SSNHL;[9–11] the virus species in these studies include herpes simplex virus (HSV), HIV, hepatitis virus, measles virus, rubella virus, mumps virus, Lassa virus, and enterovirus.[10–14] Of the suspected etiologies, viral infection is often underestimated; thus, considerable controversy exists regarding antiviral medication for treatment of SSNHL.[15] In one study, 81% of patients with SSNHL who had high titer of specific IgA to HSV-1 were improved after monotherapy with acyclovir.[16] Additionally, other studies have shown that antiviral therapy is effective in sudden deafness;[17,18] however, additional studies have reported contradictory findings.[19–21] Therefore, the effectiveness of antiviral therapy remains controversial. The question remains whether viral infection is the cause of sudden deafness. In this review, we summarized the possible relationship between viral infection and sudden deafness reported in the published literature.

Literature search

We searched the literature in the PubMed database published from January 1995 to March 2019 using the following search terms: "sudden hearing loss", "sudden deafness", and "virus". From among more than 90 related articles, all search results were merged, duplicate articles were removed, and we identified 43 articles related to our research topic. We manually searched key article reference lists to find additional related published studies.

Hypotheses

Three potential mechanisms have been proposed to explain how viral infection could lead to SSNHL. One mechanism is through viral invasion of the cochlear nerve (neuritis) or invasion of the fluid spaces and/or soft tissues of the cochlea (cochleitis). The second mechanism is via the reactivation of latent virus within tissues of the inner ear, under certain conditions. The third mechanism is through a virus indirectly triggering SSNHL, which involves a systemic or distant viral infection triggering an antibody response that cross-reacts with an inner ear antigen (an example of the immune-mediated hypothesis) or that triggers a circulating ligand, causing pathologic activation of cellular stress pathways within the cochlea (an example of the stress response hypothesis).[22]

Studies related to these hypotheses

Direct invasion

It has been estimated that 0.005% to 0.3% of people infected with mumps experience sudden deafness.[23] A much higher incidence of SSNHL following mumps (up to 4% of adult patients with mumps) has also been reported.[24] Injury of the inner ear in mumps infection may be a direct consequence of the infection. The virus reaches and infects the inner ear through the blood during viremia or through cerebrospinal fluid that reaches the perilymphatic space via the cochlear aqueduct or internal auditory meatus.[25] Animal models infected with HSV were found to have a loss of outer hair cells, fibrosis of the scala tympani and

vestibule, and atrophy of the stria vascularis and tectorial membrane. Viral capsids were found within cochlear nerve fibers (including both afferent and efferent nerve endings), and viral antigens were located throughout the cochlea. These discoveries closely resemble those in human temporal bone studies of patients with hearing loss following known infection with rubella or measles viruses.[26] Esaki et al. inoculated HSV-1 or HSV-2 directly into the middle ear in a viral labyrinthitis mouse model and demonstrated that HSV can induce sudden hearing loss and vestibular neuritis. Apoptosis of many uninfected cells in the organ of Corti were found. The authors also detected HSV antigen in the stria vascularis of the mice. This study showed that HSV infection destroyed the organ of Corti and its supporting structures, causing deafness in mice.[27] Yun et al. created an animal model by intraperitoneal injection of virus to investigate Lassa virus-induced hearing loss. Consistent with that in humans, hearing loss in surviving animals occurred in the late stages of infection or early recovery period. The authors observed mild damage in the hair cells, with the main damage visualized in the spiral ganglion neurons and vascular-rich cells within the cochlea. Lassa virus antigens were detected in the damaged areas.[28] Therefore, the virus could enter the blood circulation via intraperitoneal injection and eventually reach the inner ear, resulting in sudden hearing loss.

Virus reactivation

Ramsay Hunt-like syndrome is a typical example of virus reactivation. Varicella zoster virus remains latent in the geniculate ganglia, vestibular ganglia, and spiral ganglia after primary infection, and emerges from latency with decreased immune function to trigger facial paralysis and SSNHL. In one case of a 61-year-old woman with oral herpes lesions, bilateral hearing loss occurred but the patient had no history of herpes febrilis. The titer of IgM antibody (primary immune response antibody) against HSV-1 in her serum was not significantly elevated during the acute phase, whereas the IgG antibody (re-immune response antibody) titer was 4.46 mg/dL (normal range 0 to 0.79 mg/dL). After a period of antiviral therapy and hormone therapy, serum obtained during the convalescent stage 6 weeks after the onset of deafness showed an anti-HSV-1 IgG level of 3.28 mg/dL. These serologic markers suggested that the patient had experienced reactivation of a previously latent HSV-1 infection.[29] Psillas et al. reported a case of a 33-year-old man who developed a vesicular herpetic eruption in the external acoustic meatus and subsequent acute facial paralysis. Two weeks after his first episode of facial palsy, he experienced sudden hearing loss. Moreover, the patient's serum showed elevated levels of anti-HSV IgG and IgM.[30] Herpesviridae is considered to be the most likely etiology of SSNHL among the virus families. According to one study, 95% of adults are positive for human herpesvirus 6, 91% are HSV-1 positive, 90% are varicella zoster virus positive, 90% are positive for Epstein–Barr virus, and 70% are seropositive for cytomegalovirus.[31] These adults have been infected with these viruses when they were children; in other words, these viruses do not cause new infections in adulthood. The only explanation for sudden deafness caused by these viruses is reactivation of these latent viruses.[32]

However, there are some studies that contradict this hypothesis. Sheu found that the probability of sudden deafness within 2 months following an attack of herpes zoster is extremely low and that recent infection with herpes zoster does not increase the risk of sudden deafness. Based on basic epidemiological data, the author concluded that sudden deafness

was not associated with reactivation of this virus, except in the case of herpes zoster oticus, but sudden deafness may also be associated with hypertension and diabetes.[33]

Immune-mediated hearing loss

It has been proved that systemic events can activate the innate immune system in the cochlea, thereby producing antigens in the internal ear and triggering a strong adaptive immune response, which may result in immune-mediated hearing loss.[34] A case of a male patient with bilateral SSNHL and recurrent facial palsy owing to autoimmune disorders was first reported by Psillas et al. The patient had previously developed HSV-induced Ramsay Hunt-like syndrome. The authors believed this could possibly be the factor that triggered the patient's complex symptoms.[31] An immunologic response triggered by viral peptides develops pathogenic autoantibodies directed against phospholipids (anti-PL antibodies), especially in susceptible people. The mechanism may be the same as in the development of anti-PL antibodies among patients with idiopathic SSNHL.[35] Studies using a murine model of cytomegalovirus infection have showed that some changes can be noticed on spiral ganglion neurons and perilymphatic epithelial cells but not cochlear hair cells. Investigators have found that cochlear hair cells decreased after clearing the virus, suggesting that SSNHL induced by the virus is a result of the immune response.[36] Cashman et al. established an animal model by intramuscular injection of a virus to study Lassa virus-induced hearing loss. Consistent with pathological changes in nerve polyarteritis nodosa, tissue samples of the inner ear adjacent to the cochlear nerve displayed moderate subacute to chronic active perivascular inflammation, which multifocally surrounded smaller branches of the cochlea. These results strongly suggest that immune-mediated vasculitis-like syndrome may be the underlying cause of rapid-onset sensorineural hearing loss in patients with Lassa fever.[37]

Stress response

Adhesion molecules and cytokines play a pivotal role in the immune response in all mammalian tissues, including the inner ear.[38] Many factors, such as a systemic inflammatory disease, a viral infection, or physical, mental and metabolic stresses can cause an innate immune response, producing cytokines or reactive oxygen species (among other factors) within the inner ear.[39] The cell-mediated immune response is essential for the resolution of viral infections.[40] Spontaneous recovery from SSNHL is owing to the transient activation of the cochlear immune response. However, persistent immune activation would lead to irreversible hearing loss.[28,31,40,41] In an animal model of SSNHL associated with Lassa virus infection, it was found that unchecked expansion of the immune response to Lassa virus infection led to observed damage of the auditory nerve and the resulting loss of hearing in infected mice.[28] It has been recently shown that tumor necrosis factor alpha (TNFα) is associated with the pathogenesis of SSNHL. TNFα activates the sphingosine-1-phosphate (S1P) signaling pathway and leads to a proconstrictive state at the cochlear microcirculation.[42] Some evidence suggests that the expression of TNFα may be a prognostic factor in the treatment of sudden hearing loss using corticosteroids. A study by Zinovia et al.[43] demonstrated that reduction of TNFα during intravenous corticosteroid treatment is associated with hearing restoration. In addition, the expression of TNFα holds promise as an effective target for new methods of treating SSNHL.[43–47] A highly significant and

positive statistical interaction has been found between an increase in interleukin (IL)-6 during intravenous corticosteroid therapy and auditory rehabilitation.[43,48] IL-6 may play an antioxidative or antiapoptotic role in the process of the inner ear immune response. An increase of IL-6 may induce the expression of antiapoptotic genes.[49–51] In some cases of sudden hearing loss, Bcl family genes have led to functional reconstruction of hair cells and eventually recovery.[43] It has been suggested that various stressful life events are a cause of SSNHL, which can induce subclinical infection and/or immune system dysregulation, causing a reduction in natural killer cell activity and a rapid increase of IL-6 and neutrophils. Systemic stress also seems to be intimately involved in inducing and enhancing the activation of noradrenaline-dependent NF-kB. Increased IL-6 and neutrophils activate NF-kB in the cochlear lateral wall via IL-6 trans-signaling and ischemic stress, respectively, forming a positive feedback loop. The simultaneous activation of various NF-kB activation pathways would lead to the development of serious SSNHL.[48]

Limitations of the included studies

There are several reasons why progress in clarifying the etiopathogenesis of SSNHL is difficult to achieve. First, the present technology, including serological assessment, immunologic testing, and medical imaging, is limited in that it cannot demonstrate whether the direct etiology of SSNHL is viral. Viral infection is often diagnosed using direct or indirect technologies: the former can detect virus in infected areas of the body and the latter can assess the host immune response to infection by detecting the titer of specific antibodies. In sudden hearing loss, direct diagnosis using clinical biopsy specimens of the human inner ear is impossible because inner ear tissue is difficult to access within the temporal bone. In addition, inner ear tissue does not regenerate, so clinical biopsy could result in catastrophic sequelae. Therefore, an indirect diagnosis can often be obtained by detecting M class antibodies to identify primary infection, which is most frequently responsible for overt disease. However, pathology can be induced by an endogenous reinfection that, in most cases, would not give rise to IgM. This can lead to underestimation of the role of viruses as etiological agents in sudden hearing loss.[52] Second, sample sizes are small in most studies, and collecting data of a sufficient number of patients is difficult and time-consuming. In today's society, it is rare for people to donate their body for research after death. Moreover, cadavers from people with recent SSNHL are much rarer. Third, as we have discussed, some studies seeking evidence of a viral etiology for SSNHL are defective in their design. There are obvious technical barriers in other cases. For instance, autolysis after death, fragmentation of viral nucleic acids owing to fixation, and decalcification and potential contamination of tissues from extraneous sources during processing impede the application of PCR for postmortem temporal bone tissue in searching for evidence of viral genomic material.[53]

Conclusions

We have reviewed and summarized the relevant literature aiming to prove the etiology of SSNHL. Most studies have shown that viral infection is one etiology of SSNHL. However, there is little research proving or clearly indicating the pathogenesis of this disease. Thus, further research is needed to elucidate the precise etiopathogenesis of SSNHL to enable better understanding of

the disease and establish more suitable treatment to restore patients' hearing.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Xin Chen https://orcid.org/0000-0002-4041-9960

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