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Recent pathogenetic aspects of hearing loss in COVID: A literature review

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Abstract. The World Health Organisation predicts that by 2050, up to 10% of the world's population will need rehabilitation to address disability-related hearing loss. The purpose of this study was to identify the main mechanisms of hearing loss associated with Severe Acute Respiratory Syndrome Coronavirus 2 infection. The study included modern English-language scientific publications, mainly those with a high citation index, through the professional platforms MEDLINE/PubMed and Index Medicus. A total of 48 sources were selected. Research papers devoted to the development of conductive or sensorineural hearing loss, which occurred directly as a result of a viral disease, or is associated with the processes that accompany it (treatment, concomitant pathology, vaccination, etc.), were analysed. It was found that the development of viral-induced hearing loss in COVID has a multifactorial nature. The heterogeneity of audiological changes is primarily conditioned by direct viral damage to auditory analyser cells that express membrane receptors of the angiotensin-converting enzyme of the second type. In addition, there is a reactivation of latent viral infection, extravasation of exudate into the middle ear cavity, blood clotting disorders, immune-mediated cell damage, local and generalised inflammatory reactions that affect both sound conduction and sound perception in one ear or both. Some cases of audiological disorders may also be of iatrogenic origin, since post-vaccination complications and ototoxic effects of medications used in the treatment of COVID-19 are not excluded, which should be considered by clinicians at all levels of healthcare to effectively manage a specific clinical scenario

Keywords: audiology; conductive hearing loss; sensorineural hearing loss; coronavirus; ototoxicity; vaccination

INTRODUCTION

The problem of hearing loss is one of the most pressing for the global medical community. More than 430 million people on the planet require rehabilitation for hearing loss, which leads to disability [1]. There are 34 million children among them. 25% of adults over the age of 60 need rehabilitation. According to forecasts of the World Health Organisation (WHO), by the middle of the 21st century, hearing loss can be diagnosed in 2.5 billion people, and at least 700 million of them will need rehabilitation. However, timely and effective treatment prevents the development of hearing loss in 60% of cases in both children and adults, especially when it is caused by exposure to noise or ototoxic drugs.

One of the causes that can cause hearing loss is viral infections, including intrauterine ones. J. Saniasiaya [2] indicates that viral infection is a recognised aetiological factor of hearing loss, which varies significantly depending on the type of causal virus: from mild to deep deafness, can be conductive or sensorineural, unilateral or bilateral, reversible and non-reversible. The prognosis is influenced

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not only by the morphological and virulent properties of the pathogen, but also by the use of specific antiviral drugs.

X. Shi *et al.* [3] describe the pathogenesis of audiological disorders in infection with cytomegalovirus, herpes simplex or herpes zoster viruses, influenza, Epstein-Barr viruses, Zika, Lassa, enteroviruses, and many others.

The first quarter of the 21st century was marked by outbreaks of coronavirus infections. In 2003, the disease with a predominant lesion of the respiratory system and a high mortality rate was called SARS-CoV – Severe Acute Respiratory Syndrome-related COronaVirus. The names of the next two epidemics reflected their geographical and temporal features. In 2012, the first cases of MERS-CoV – Middle East Respiratory Syndrome COronaVirus were recorded in the Arabian Peninsula, and COVID-19 or coronavirus disease ("COronaVIrus Disease" SARS-CoV-2) was first described in 2019 [4]. The latter, according to the statement of WHO Director-General Tedros Adhanom Gebreyesus dated May 5, 2023 [5], although it no longer has the status of an emergency, does not cease to pose a threat.

From its first days, as in the previous two, the main attention was focused on respiratory manifestations. But there are steadily increasing reports of the prevalence and diversity of sensory disorders [6] and hearing loss [7] associated with COVID-19. In particular, K.M.C. Ong *et al.* [8] noted that most individuals included in their review and had auditory and vestibular disorders, within one month of positive diagnostic tests for SARS-CoV-2 or clinical confirmation of this infection, began to experience hearing loss. In addition, sensorineural hearing loss was sudden in 23.1% of cases. According to the recommendations of the American Academy of Otolaryngology–Head and Neck Surgery, sudden sensorineural hearing loss (SSNHL) occurs within 72 hours and is a hearing loss of ⩾30 dB on at least 3 consecutive frequencies [9].

An active vaccination campaign against coronavirus has led to an increase in researchers' interest in a possible link between it and the occurrence of otological symptoms. However, their claims are quite ambiguous, especially regarding the frequency, severity, and prognosis of hearing loss. H. Wichova *et al.* [10] reported the occurrence of tinnitus and vertigo in patients shortly after vaccination, and an increase in cases of newly diagnosed idiopathic sensorineural hearing loss doubled over a 30-day period in 2021 compared to the same period in 2019 and 2020.

In contrast, E.J. Formeister *et al.* [11], based on the analysis of the results of a survey of more than 86 million people vaccinated against SARS-CoV-2 in the United States in the winter of 2020-2021, found that the incidence of sudden SARS-CoV-2-induced sensorineural hearing loss after immunisation did not exceed those inherent in the general population.

The growing number of long-term consequences of COVID-19 [12] and not encouraging forecasts regarding the weakening of the virulent properties of the virus encourage [13] the search for modern effective methods of their prevention and treatment at all stages of medical care, from primary care physicians to specialised otolaryngological and sign language practice. And this, in turn, requires a clear understanding of the mechanisms of occurrence and development of audiological disorders. That is why the purpose of the study was to investigate the main mechanisms of hearing loss associated with SARS-CoV-2, based on world experience, by analysing available information and literature sources.

To achieve this goal, the authors analysed scientific publications mainly with a high citation index published in English in 2018-2024. The search was conducted in January 2024 using electronic database of medical and biological publications MEDLINE/PubMed. Keywords in English were used to search for potentially relevant materials: "COVID" and "Hearing Loss" (378 publications) or "SARS-CoV-2" and "Hearing Loss" (181 publications), followed by a selection of papers that met the chosen goal. A total of 48 scientific sources were selected. Later additions to the review included five papers, which were published after January 2024 and were discovered after the initial screening. In particular, the main criteria for inclusion in the systematic review and meta-analysis were: established SARS-CoV-2 infection; vaccination or treatment of this infection, first-time detected sensorineural or conductive hearing loss, and temporal correlation between the two events.

SARS-COV-2-INDUCED CONDUCTIVE HEARING LOSS

Viruses can infect and cause inflammation of the middle ear cavity. Inflammatory oedema and increased permeability of the vascular wall lead to exudate effusion into its cavity and, as a result, cause conductive hearing loss. The role of coronaviruses in the development of the inflammatory process of the middle ear has been known for more than 20 years [14]. At the beginning of the development of the coronavirus pandemic, this problem was not widely covered. It can be assumed that this is due to difficulties in establishing a diagnosis during strict epidemiological measures, a large number of asymptomatic cases of the disease, or the fact that respiratory and other manifestations of the disease came to the fore. However, there have been isolated reports and their number is growing.

Sound conduction can change as a result of the upward spread of infection from the nasopharynx, which leads to exudation into the middle ear cavity, otitis media, otalgia, and tinnitus [15]. Colonisation of the middle ear and mastoid process by SARS-CoV-2 at the beginning of the pandemic was detected during autopsy [3, 16]. Therefore, the question remained whether SARS-CoV-2 migrated to the middle ear of living patients during or possibly after primary infection, or whether it passively entered the ear post mortem [17].

In 2021, N. Raad e*t al.* [18] described clinical cases of eight patients with otitis media who were treated in two specialised clinics in Iran in April and May during the COVID-19 pandemic. All of them had no previous history of otolaryngological pathology and all of them were confirmed to be infected with coronavirus. In addition, according to the authors, the atypical time of occurrence of the problem is in favour of SARS-CoV-2-induced inflammatory process of the middle ear: in the spring and summer period, the incidence of otitis media is usually the lowest, and its peak occurs in autumn and winter. Five of the patients had clinical signs of SARS-CoV-2-related damage to other organs (cough, shortness of breath, fever, etc.), which was confirmed by instrumental studies. Two had concomitant chemosensory dysfunction. The case of a young woman who, after contact with a COVID-19 patient, experienced

only ear pain and hearing loss without any systemic manifestations of infection is interesting. Examination of the ear revealed an effusion in the middle ear on the left, fluid/air level, and severe eardrum swelling. The result of a polymerase chain reaction (PCR) smear from the oropharynx for COVID-19 was negative; however, a PCR test for COVID-19 with middle ear fluid was positive. All patients were successfully treated. A thorough analysis indicated that otitis media, which develops as a result of exudation and a decrease in pressure in the middle ear cavity, may be both one of the symptoms of COVID-19 and its complication.

S. Bhatta *et al*. [19] investigated the presence of conductive hearing impairment in 331 patients with COVID-19 at nine institutes in India and Nepal between July 01, 2020 and April 30, 2021. The criteria for inclusion in the study were not only the absence of appropriate pathology in the anamnesis, in addition, age was taken as a factor in the development of presbyacusis in older people and excessive subjectivism in the examination of children, and specific treatment for COVID-19, considering its potential ototoxicity. According to their results, only 11.2% of patients independently complained of audiological symptoms (tinnitus, hearing loss, otalgia, etc.), considering them the main ones, and 88.8% of patients noticed them only after a questionnaire and examination [19]. The most standard method for quantifying the sensitivity of an auditory analyser is tonal threshold audiometry. The degree of hearing loss is determined by the thresholds of auditory perception in the frequency range from 500 to 4,000 Hz, that is, at the so-called speech frequencies (Table 1).

Table 1. Severity of hearing loss based on audiogram metrics

Hearing Range	dB
Normal	-10 – 25
Mild	26 – 40
Moderate	41 – 55
Moderately Severe	56 – 70
Severe	70 – 90
Profound	91+

Source: [20]

According to S. Bhatta *et al*. [19], when audiometric testing with pure tone, a conductive type of hearing loss of up to 40 dB was found in 3.2% of patients with COVID-19. And the registration of tympanograms of type B and C in a number of patients indicated the presence of Eustachian tube dysfunction. The patients' hearing recovered after 3 months.

Subsequently, Y. Fan *et al*. [21] found that almost 70% of fluid samples obtained from the middle ear cavity in patients with COVID-19 were PCR-positive for SARS-CoV-2. This allowed the researchers to suggest that exudative otitis media may also be a symptom of coronavirus disease. This assumption was confirmed by the result of treatment: complete recovery was observed in 40.7%, and 51.9% of patients were diagnosed with hearing improvement, which averaged 14.5 ± 8.1 dB, with an average decrease in the airbone interval by 13.5 ± 9.0 dB. Similar data were found for infection with the Omicron strain [22, 23], in which the incidence of otitis media increased by 15% [24]. Thus, SARS-CoV-2 can infect the middle ear cavity and cause an inflammatory response. Oedema, exudation into the tympanic cavity or mastoid cells, and auditory tube dysfunction impair sound conduction and, as a result, lead to hearing loss.

CLINICAL CHARACTERISTICS OF SARS-COV-2-INDUCED SENSORINEURAL HEARING LOSS

The relation between sensorineural hearing loss and COVID-19 was first noticed by W. Sriwijitalai & V. Wiwanitkit [7] back in spring 2020. And over time, the possibility of a negative impact of the virus on the cells of the inner ear began to attract more and more attention. V. Fancello *et al.* [25] in their study found that sensorineural hearing loss (SNHL) can occur both during and after SARS-CoV-2 infection. In addition, in 12.7% of patients, this is described as an isolated symptom; while in the majority (87.3%), hearing loss was accompanied by other additional signs. Among them, tinnitus prevailed (100%); vertigo was noted in almost half of the patients (45.5%); and facial palsy – in 5.5%. The researcher focuses on three cases when the lesion of the n. facialis had a clear connection with SNHL. Chemosensory dysfunction has also been described in 25% of patients with perceptual hearing loss: anosmia, hyposmia, ageusia, and dysgeusia. These changes were confirmed by radiological diagnostic data indicating lesions of the cochlea, cranial nerves VIII and/or VII, haemorrhagic lesions of the brain parenchyma, intra-labyrinth micro-hemorrhages, numerous cochlear fibrosis foci, etc. In 75% of cases, otoacoustic emission (OAE) results indicate possible damage to the outer hair cells. In this study, a fairly wide range of hearing loss was found: 58.7% of patients had mild to moderate hearing loss, 4.8% had moderate to severe hearing loss, and 36.5% had severe to deep hearing loss (Table 2).

Table 2. Severity of hearing loss in the patients included in the study

Hearing Range	Degrees of sensorineural hearing loss
Mild	20.6%
Mild – Moderate	6.3%
Moderate	31.7%
Moderate – Severe	4.8%
Severe	11.1%
Severe – Profound	20.6%
Profound	4.8%

Source: [25]

The positive effect of treatment (improvement of hearing from mild to almost complete recovery) was achieved in more than a third of patients. At the same time, the return of hearing acuity to the initial level (before infection with coronavirus) was observed only in 12.5% of cases [25]. A similar trend has been confirmed in other studies.

However, it is not always possible to establish a timely link between the sudden onset of hearing loss in the acute period of COVID. Most patients are hospitalised in the intensive care unit or are isolated during this period, and there is a potential risk of infection, which in combination makes impossible a performing of comprehensive audiological examination. Therefore, SNHL detection is often delayed [9], which negatively affects the urgency of prescribing adequate treatment and prognosis. According to J. Jeong *et al.* [6], in only one in ten patients, the first signs

of infection were hearing loss, tinnitus, or dizziness. The vast majority of people reported fever, cough, shortness of breath, or fatigue 21 days before the onset of audiological symptoms. In addition, after the SNHL was detected, typical general manifestations of the disease continued for another 2 weeks. Even in the latent course of the disease, in the absence of obvious clinical signs, changes in the thresholds for perception of high-frequency pure tone and OAE amplitude indicate a damaging effect of SARS-CoV-2 on hair cell function [26].

Chemosensory manifestations of coronavirus disease confirm the neuroinvasiveness of SARS-CoV-2. According to V. Fancello *et al.* [25], the site of entry of the virus into the central nervous system may be the olfactory nerve, since a quarter of patients with SARS-CoV-2-induced perceptual hearing loss reported certain changes in taste and smell, while symptoms of viral damage to the facial nerve were observed 5 times less often. Changes detected in magnetic resonance imaging (MRI) of the brain also indicated the involvement of *n. vestibulocochlearis* and *n. facialis*.

Signs of damage to these nerves, confirmed by MRI results, are described by J. Jeong, *et al.* [6]: 30% of patients showed signs of virus entry into the central nervous system; 20% had dysgeusia and anosmia. In their opinion, in these patients, the most likely spread of the virus through the cerebrospinal fluid to the cranial nerves, and subsequently to the inner ear.

Damage to the sensory systems, including the auditory system, occurs in most people infected with coronavirus. In clinical practice, tonal audiometry is mainly used to determine the presence of hearing loss. To substantiate the causal relationship between hearing loss and damage to the cells of the organ of Corti, auditory pathway or auditory cortex, the results of otoacoustic emission, registration of acoustic reflexes, auditory evoked potentials, radiological examinations, etc. are needed, timely implementation of which at the beginning of the disease is not always possible. Delayed diagnosis and, consequently, treatment may be one of the factors that slow down and complicate the full recovery of hearing in some patients. The results of diagnostic tests are often ambiguous and require careful interpretation, considering the understanding of the pathophysiology of this disease.

PATHOGENETIC ASPECTS OF SARS-COV-2-INDUCED SENSORINEURAL HEARING LOSS

Possible mechanisms for the development of virus-induced sensorineural hearing loss and other audiological or vestibular disorders can be divided into direct and indirect mechanisms. Direct viral cytotoxicity is directed at the cells of the inner ear, in particular, the spiral organ and vestibulocochlear nerve. Activation of inflammatory mechanisms, neuroinflammation, and secondary immune-mediated processes play a significant role in damage to these structures. The reactivation of latent viral infection in the inner ear is also of some importance [27]. It is not only the cells of the inner ear that are susceptible to coronavirus; this virus can affect the auditory pathway in different parts of it (Fig. 1).

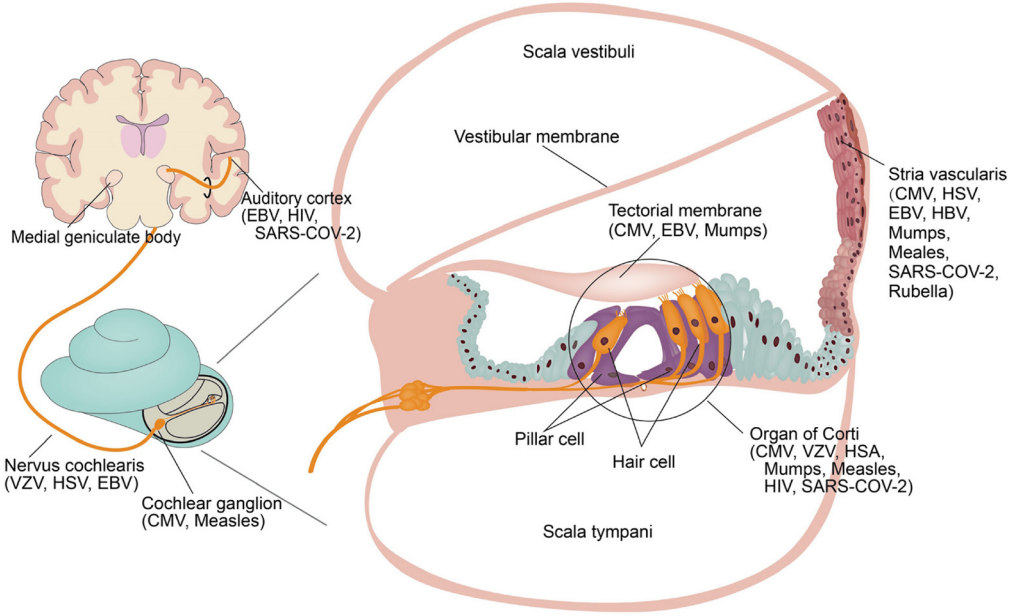

Figure 1. Schematic diagram of the infected area of the virus in the auditory pathway

Source: [3]

Nerve cell damage and the clinical manifestation of this process are observed both during the acute phase of infection and after it. Current understanding of the mechanisms of neurological symptoms remains imperfect. Most likely, the occurrence and progression of SNHL is characterised by multifactorial nature, when the key is not only the variety of additional contributing factors and mechanisms, but also the variability of their combination. These are primarily direct viral invasion/damage, hypoxia, immune-mediated damage, and blood clotting disorders [25, 28].

In the process of viral infection and further development of the disease, a significant role is played by the

unequal organ expression of specific receptors on the membranes of target cells and the selective sensitivity of viruses to them. For the coronavirus, the angiotensin-converting enzyme 2 receptor (ACE2) located on the human cell membrane is a necessary binding component for its Spike protein to the human cell [29]. W. Ni *et al.* [30] explain the lack of specific and diverse extrapulmonary symptoms in COVID-19 by the fact that these receptors are present on the cell membranes of many human organs. The SARS-CoV-2 adhesive protein binds to the host cell's ACE2 receptor. For further penetration of the virus into the cell, hydrolysis and cleavage of the ACE-2 protein by transmembrane protein serine 2 (TMPRSS2) are required [31].

The development of audiological symptoms is also associated with the high affinity of SARS-CoV-2 for ACE2, which is widely represented in cochlear hair cells, on the membranes of middle ear cells, and Eustachian tube cells (Fig. 1) [32]. In addition, adult inner ear cells in addition to ACE2 receptors, according to J. Jeong *et al.* [6] also express the cofactors TMPRSS2 and FURIN, which are necessary for the virus to enter the cell.

Functional changes or damage, including viral damage, to the outer hair cells are confirmed by the results of otoacoustic emission (OAE), during which, in response to stimulation with a signal of a certain frequency, a sound created by the displacement of the cochlear basilar membrane from the base to the apex is recorded [33]. Internal hair cells, which numbers are three times smaller, form synapses of 90-95% of the auditory nerve fibres and transmit almost all acoustic information to the brain [34]. It would be logical to assume that they also undergo changes, but it is not yet possible to clinically determine their functional state (Fig. 2).

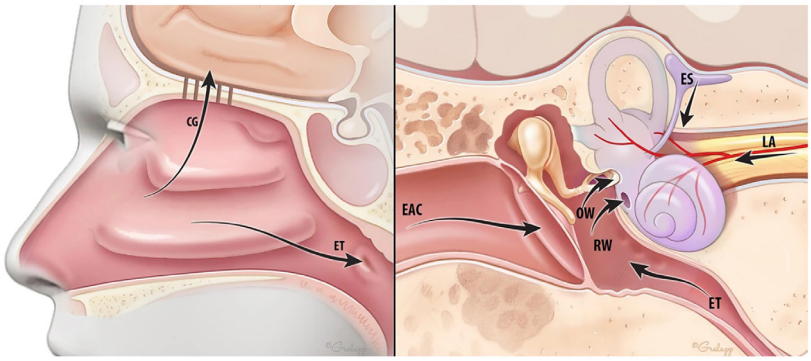

Figure 2. Potential paths for SARS-CoV-2 entry into the inner ear

Source: [6]

SARS-CoV-2 can enter the inner ear in several ways. The first pathway – through the nose and olfactory sulcus of the frontal lobe (lat. *sulcus olfactorius lobi frontalis*) to the central nervous system, as shown above in patients with chemosensory symptoms. The second pathway – through the endolymphatic sac (lat. *saccus endolymphaticus*), it is indicated by the abbreviation ES in Figure 2. Functionally, it is an immunological interface for the inner ear and regulates its fluid level. The proof of this postulate is the stated reverse development of SNHL. That is, some patients developed hearing loss due to endolymphatic hydrops due to the penetration of SARS-CoV-2 through the endolymphatic sac [6].

Third possible path – haematogenic. The virus spreads through the vascular tissue (lat. *stria vascularis*), between the epithelial cells of which a network of capillaries passes. The stria vascularis is the only structure in the spiral organ that concentrates enzymes, ensures the diffusion of ions and other substances both in and out of the endolymph. Its damage disrupts the potassium homeostasis of the cochlear endolymph and endocochlear potential. In addition, systemic inflammation increases vascular permeability, for example *arteria labyrinthi*, which in Figure 2 is indicated by the abbreviation LA. This can promote the penetration of the virus and pro-inflammatory cytokines into the inner ear. SARS-CoV-2 can damage the blood-brain barrier, and the blood-brain and blood-labyrinth barriers are structurally and functionally similar (Fig. 1, Fig. 2) [35, 36]. It can be assumed that this pathway is most likely for patients with severe COVID-19, who are characterised by uncontrolled and excessive cytokine secretion, the so-called "cytokine storm". According to the haematogenic theory described by J. Saniasiaya [2], the coronavirus attaches to haemoglobin via the β-chain, enters red blood cells, which become a kind of viral transporter, that is, spread through the blood, infecting all tissues that express ACE2.

The fourth pathway – SARS-CoV-2 penetration through the membranes of the round (abbreviation RW in Fig. 2) or oval (abbreviation OW in Fig. 2) windows. This assumption is based on data on colonisation of the mastoid process and middle ear by SARS-CoV-2 [37]. However, the likelihood of this pathway being implemented seems to be low, given the absence of signs of infection and exudation into the tympanic cavity.

A significant amount of ACE2 is found on the membranes of medulla oblongata cells, in the brain, in particular in the temporal lobe. It is in the temporal lobes of the cerebral cortex that the central (cortical) part of the auditory analyzer, the so-called auditory cortex, is located, the defeat of which also leads to perceptual hearing loss. After amplification, SARS-CoV-2 leaves the host cell and inoculates into cells of the auditory cortex that express a large number of ACE2 receptors, which, in turn, leads to hearing loss (Fig. 1) [3, 38]. Contact of the virus with the surface receptors of the temporal lobe triggers the release of inflammatory mediators, including cytokines, which are also capable of direct cell damage, that is, they deepen functional and structural changes in brain cells [2].

Among the mechanisms that lead to sudden sensorineural hearing loss, J. Saniasiaya [2] indicated not only inflammation of the auditory pathway from the cochlea to the auditory cortex, cross-reaction between inner ear cells and viral antigens, and negative effects on perilymphatic tissue. Of great importance is deoxygenation of red blood cells under the influence of coronavirus, and, as a result, constant hypoxia of the auditory cortex neurons.

Another likely hypothesis of hearing loss is reduced perfusion of the hearing organs due to ischaemia. According to R. Knight *et al.* [39], the incidence of arterial and venous thromboembolic events remains quite significant even 49 weeks after the diagnosis of COVID-19. If increased blood clotting in the veins is clinically manifested mainly by pulmonary embolism, deep vein thrombosis, usually in the legs, etc., then arterial thrombosis leads to ischemia and tissue necrosis. This hypothesis is supported by elevated levels of D-dimer in the blood and microthrombosis in SARS-CoV-2 infected individuals with audiological symptoms [40].

Figure 3 illustrates the diversity of localisation of potential thrombosis, which can lead to the development of audio-vestibular disorders due to arterial occlusion. For example, increased coagulation in the terminal capillary bed, which starts from the labyrinth artery and provides vascularisation of the inner ear, leads to cochlear SNHL [41]. Even temporary hypoxia has a stressful effect on the inner ear cells, increasing the concentration of reactive oxygen species, which can cause additional damage to hair cells. On the other hand, a blood clot in one of the vessels feeding the upper auditory pathways can lead to central hearing loss [40].

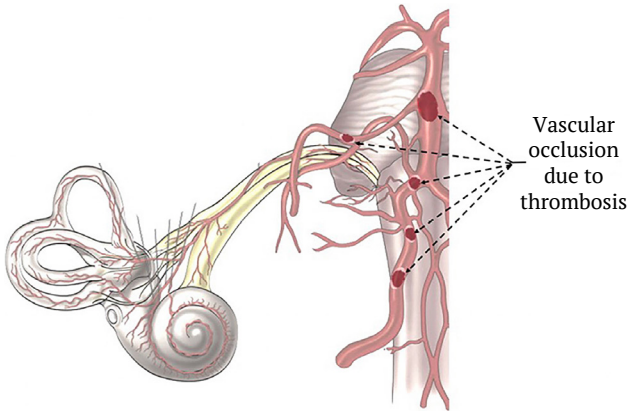

Figure 3. Indirect Virus Effect
Source: [40]

Changes in the blood clotting rate can cause both macro- and/or microthrombosis [42], followed by transient or permanent ischaemia/hypoxia in the auditory pathways, and the development of haemorrhagic complications, such as intra-labyrinth haemorrhage [43] or haemorrhagic lesions of the brain parenchyma [25], which also determines the onset, duration, and prognosis of audiological disorders. Virus-induced sensorineural hearing loss may result from direct viral damage, inflammation, and secondary effects like ischemia and thrombosis.

OTHER ETIOLOGICAL AND PATHOPHYSIOLOGICAL FACTORS OF HEARING LOSS NOT ASSOCIATED WITH THE DIRECT ACTION OF THE SARS-COV-2 VIRUS

From the first days of the fight against SARS-CoV-2, A. Ciorba *et al.* [44] focused the attention of the world medical community on the ototoxicity of certain drugs. In particular, chloroquine and hydroxychloroquine can cause sensorineural hearing loss or tinnitus, which are rarely reversible, especially if these drugs are used for weeks or months. The use of macrolide antibiotic azithromycin can also cause both reversible and irreversible sensorineural hearing loss and tinnitus, and it has often been used in combination with hydroxychloroquine to enhance the effect. And in some countries, ototoxic chloroquine and hydroxychloroquine were administered to treat SARS-CoV-2 infection at doses significantly higher than those used to treat malaria [45].

The fact that potentially ototoxic furosemide, antiviral analogues of adenosine nucleotides (remdesivir and favipiravir), and the nucleoside reverse transcriptase inhibitor lopinavir, which are associated with the occurrence of perceptual hearing loss after several weeks of administration, were used in the treatment of patients with COVID-19. The ototoxic effect of lopinavir has also been confirmed *in vitro* [25, 44]. The severity of audiological symptoms usually depends on the dose of the drug, the duration of therapy, comorbidity, and the use of other medications that may potentiate negative effects or have synergistic effects when used in combination or sequentially.

Cochlear hair cells, which have a high metabolic activity and are particularly sensitive not only to toxic, but also to hypoxic or ischemic effects, are considered the most vulnerable [44]. That is, their damage is possible both as a result of blood clotting disorders, and persistent hypoventilation and hypoxygenation in the presence of SARS-CoV-2 associated respiratory or cardiovascular pathology. In addition to significant advances in the treatment of SARS-CoV-2-related diseases, a landmark event in the fight against the virus was that some COVID-19 vaccines became commercially available in the first half of 2021. However, their use had its own risks.

F. Zoccali *et al.* [46] provide stories of a 40-year-old man and a 67-year-old woman who developed audio-vestibular disorders after the third dose of the vaccine. In man – after five days (Pfizer-BioNTech vaccine), and in woman – after seven days (Moderna vaccine). The appearance of dizziness, tinnitus, and sudden perceptual hearing loss (a unilateral increase in audiometric thresholds in a man was up to 70 dB, in a woman – up to 60 dB at each frequency), was attributed to a possible cross-immune response between the components of the vaccine and human host cells, a possible spasm of the internal auditory artery or increased blood clotting, which leads to thrombosis. Ultimately, the structures of the inner ear are very sensitive to circulatory disorders and ischaemia, which are one of the main causes of sudden idiopathic sensorineural hearing loss.

M. Canales Medina & M. Ramirez Gómez [47] also described clinical cases of newly identified postvaccinal tinnitus and acute sensorineural hearing loss. In most of the patients, these symptoms appeared a few days after the second

dose of the Astra Zeneca vaccine was administered. Hearing loss ranged from mild to severe, which was confirmed by the results of tonal audiometry. The researchers note a positive effect of the use of systemic corticosteroids to restore hearing in this cohort of patients. The researchers point to a decrease in perfusion and ischaemia of the hearing organs as a result of increased thrombosis caused by the Astra Zeneca vaccine from COVID-19 as the most likely hypothesis regarding the pathogenesis of audiological changes.

Discussing the possible link between vaccination and sudden sensorineural hearing loss, J. Jeong & H.S. Choi [48] suggested that viral antigens after vaccination, leading to the development of antibodies and the release of cytokines, can trigger autoimmune immunocomplex mediation against cells of spiral organ. Additionally, immune and inflammatory responses can lead to vasculitis and vascular ischaemia. The immunosuppressive and anti-inflammatory effects of corticosteroids, which are effectively used in the treatment of such patients, are also considered. In order to prevent post-vaccination complications, researchers [46, 48] suggest that instead of using systemic steroids, intratympanic steroids should be considered, which will suppress the systemic immune response to a much lesser extent.

Analysing the effect of vaccine immunisation on the degree of hearing loss, X.W. Liew *et al*. [20] determined the thresholds of auditory perception in pure tone audiometry. According to their results, the association between vaccination and sensorineural hearing loss (SNHL) is insignificant. In most patients, with effective treatment, hearing was restored to normal levels within a few weeks or months. According to the researchers, the incidence, prevalence, and post-vaccination occurrence of SNHL in most countries remains insignificant and is likely to remain unchanged over time. Some mechanisms of development of post-vaccination hearing loss, including delayed hearing loss, remain to be elucidated. There are assumptions about a certain effect (payload) of mRNA and an autoimmune mechanism, such as the response to the lipid nanoparticle delivery agent, and the production of immunoglobulin G in the 10-14-day period after vaccine administration, which coincides with the period of occurrence of SNHL after vaccination.

For over 20 years, the SARS-CoV-2 virus has been challenging doctors around the world: the absence of specific symptoms and the ability to prolong them, the heterogeneity of pathophysiology and multiorgan damage, and the absence of a decrease in virulence with mutation – this is not a complete list of its diversity. Hearing loss is only one of the symptoms of its harmful effects on the human body, which requires the search for new approaches in prevention, treatment, and diagnosis, since timely and effective detection of changes is an undoubted condition for significantly reducing risks. Patients with SARS-CoV-2 are completely isolated during the disease, which complicates, and sometimes makes it impossible, both otoscopic and audiometric diagnostics. This problem could be solved by developing methods for remote audiological monitoring, which is one of the challenging tasks of the future.

CONCLUSIONS

This study successfully analysed the main mechanisms by which SARS-CoV-2 infection leads to hearing loss. Despite a fairly high awareness of the aetiopathogenesis of virus-induced processes, this pandemic has become an unprecedented case in modern history and medical practice. In the pathogenesis of hearing loss caused by SARS-CoV-2, in addition to direct viral and immune-mediated damage to cells of both sound conduction and sound perception processes, a number of mediated mechanisms are distinguished. The conductive component of the disorder is mainly a consequence of an inflammatory reaction, swelling and exudation into the middle ear cavity, which are potentiated by impaired ventilation of the auditory tube.

The sensorineural component of hearing loss, in most cases, is the result of direct viral cytotoxicity directed at auditory pathway cells with high expression of angiotensin-converting enzyme 2 receptors. Damage to the hair cells of the cochlea, auditory pathway cells, and cortex is further aggravated by local and generalised inflammatory reactions, venous and arterial thrombosis, with subsequent tissue ischaemia, hypocoagulation, hypoperfusion, etc. Ototoxic medications used in the treatment of COVID patients, especially with their long-term and combined use, comorbidity and polypharmacotherapy, have an additional negative effect on auditory function. The influence of COVID vaccines as a probable etiological factor in the development of sensorineural hearing loss was investigated. Diagnosis of hearing disorders after COVID-19 includes audiometry (determination of audibility thresholds), otoacoustic emission (assessment of the function of external hair cells) and, in some cases, magnetic resonance imaging (MRI) to detect structural changes in the brain.

The results of the study are important for clinical practice. They highlight the need for early diagnosis and treatment of hearing disorders in patients who have had COVID-19. In addition, the data obtained can be used to develop new methods for the prevention and treatment of these disorders. Further research is needed to investigate the long-term effects, develop new treatments and prevention, and create effective rehabilitation systems. A multidisciplinary approach involving collaboration between otolaryngologists, neurologists, immunologists, and other professionals is essential for the successful treatment of patients with COVID-19-related hearing disorders. It is also important to consider the economic and social consequences of hearing loss, and to develop social adaptation programmes for such patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Deafness and hearing loss [Internet]. [cited 2024 Apr 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

[2] Saniasiaya J. Hearing loss in SARS-CoV-2: What do we know? Ear Nose Throat J. 2021;100(Suppl 2):152S–54S. DOI: 10.1177/0145561320946902

[3] Shi X, Liu X, Sun Y. The pathogenesis of cytomegalovirus and other viruses associated with hearing loss: Recent updates. Viruses. 2023;15(6):1385. DOI: 10.3390/v15061385
[4] Kaul R, Devi S. Coronavirus – a crippling affliction to humans. Recent Pat Biotechnol. 2022;16(3):226–42. DOI: 10.2174/1872208316666220404103033
[5] WHO Director-General's opening remarks at the media briefing – 5 May 2023 [Internet]. [cited 2024 Apr 30]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-may-2023
[6] Jeong J, Ocwieja KE, Han D, Wackym PA, Zhang Y, Brown A, et al. Direct SARS-CoV-2 infection of the human inner ear may underlie COVID-19-associated audiovestibular dysfunction. Commun Med. 2021;1:44. DOI: 10.1038/s43856-021-00044-w
[7] Sriwijitalai W, Wiwanitkit V. Hearing loss and COVID-19: A note. Am J Otolaryngol. 2020;41(3):102473. DOI: 10.1016/j.amjoto.2020.102473
[8] Ong KMC, Cruz TLG. Otologic and vestibular symptoms in COVID-19: A scoping review. World J Otorhinolaryngol Head Neck Surg. 2022;8(4):287– 96. DOI: 10.1002/wjo2.57
[9] Chandrasekhar SS, Tsai Do BS, Schwartz SR, Bontempo LJ, Faucett EA, Finestone SA, et al. Clinical practice guideline: Sudden hearing loss (update). Otolaryngol Head Neck Surg. 2019;161(Suppl 1). DOI: 10.1177/0194599819859885
[10] Wichova H, Miller ME, Derebery MJ. Otologic manifestations after COVID-19 vaccination: The House Ear Clinic experience. Otol Neurotol. 2021;42(9):e1213–e18. DOI: 10.1097/MAO.0000000000003275
[11] Formeister EJ, Chien W, Agrawal Y, Carey JP, Stewart CM, Sun DQ. Preliminary analysis of association between COVID-19 vaccination and sudden hearing loss using US Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System data. JAMA Otolaryngol Head Neck Surg. 2021;147(7):674–76. DOI: 10.1001/jamaoto.2021.0869
[12] O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine. 2022;55:101762. DOI: 10.1016/j.eclinm.2022.101762
[13] Lin X, Sha Z, Trimpert J, Kunec D, Jiang C, Xiong Y, et al. The NSP4 T492I mutation increases SARS-CoV-2 infectivity by altering non-structural protein cleavage. Cell Host Microbe. 2023;31(7):1170–84.e7. DOI: 10.1016/j.chom.2023.06.002
[14] Massa HM, Cripps AW, Lehmann D. Otitis media: Viruses, bacteria, biofilms and vaccines. Med J Aust. 2009;191(Suppl 9):S44–S49. DOI: 10.5694/j.1326-5377.2009.tb02926.x
[15] Fidan V. New type of coronavirus induced acute otitis media in adult. Am J Otolaryngol. 2020;41(3):102487. DOI: 10.1016/j.amjoto.2020.102487
[16] Cure E, Cure MC. Comment on "Hearing loss and COVID-19: A note". Am J Otolaryngol. 2020;41(4):102513. DOI: 10.1016/j.amjoto.2020.102513
[17] Rubicz N, Poier-Fabian N, Paar C, Winkler-Zamani M, Hermann P, Raidl S, et al. SARS-CoV-2 in the middle ear-CovEar: A prospective pilot study. J Pers Med. 2023;13(6):905. DOI: 10.3390/jpm13060905
[18] Raad N, Ghorbani J, Mikaniki N, Haseli S, Karimi-Galougahi M. Otitis media in coronavirus disease 2019: A case series. J Laryngol Otol. 2021;135(1):10–13. DOI: 10.1017/S0022215120002741
[19] Bhatta S, Sharma S, Sharma D, Maharjan L, Bhattachan S, Sah MK, et al. Study of hearing status in COVID-19 Patients: A multicentered review. Indian J Otolaryngol Head Neck Surg. 2022;74(Suppl2):3036–42. DOI:10.1007/s12070-021-02710-w
[20] Liew XW, Tang ZHM, Ong YQC, See zKC. Hearing loss after COVID-19 and non-COVID-19 vaccination: A systematic review. Vaccines. 2023;11:Y, Chen X. Presence of SARS-CoV-2 in middle ear fluid and characterization of otitis media with effusion in patients 1834. DOI: 10.3390/vaccines11121834
[21] Fan Y, Gao R, Shang Y, Tian X, Zhao with COVID-19. Int J Infect Dis. 2023;136:44–48. DOI: 10.1016/j.ijid.2023.08.024
[22] Han C, Wang H, Wang Y, Hang C, Wang Y, Meng X. The silent reservoir? SARS-CoV-2 detection in the middle ear effusion of patients with otitis media with effusion after omicron infection. Am J Otolaryngol. 2024;45(3):104229. DOI: 10.1016/j.amjoto.2024.104229
[23] Fu X, Wang Z, Chen B, Sun H, Lyu J, Shao J, et al. Detection of SARS-CoV-2 virus in middle ear effusions and its association with otitis media with effusion. J Med Virol. 2024;96(3). DOI: 10.1002/jmv.29545
[24] Liang X, Zhang B, Ding Y, Guan Y, Zhou P, Deng Y, et al. Clinical observation of otitis media secretory during COVID-19. Otol Neurotol. 2024;45(5):475–81. DOI: 10.1097/MAO.0000000000004158
[25] Fancello V, Fancello G, Hatzopoulos S, Bianchini C, Stomeo F, Pelucchi S, Ciorba A. Sensorineural hearing loss post-COVID-19 infection: An update. Audiol Res. 2022;12(3):307–15. DOI: 10.3390/audiolres12030032
[26] Mustafa MW. Audiological profile of asymptomatic COVID-19 PCR-positive cases. Am J Otolaryngol. 2020;41(3):102483. DOI: 10.1016/j.amjoto.2020.102483
[27] Chen X, Fu YY, Zhang TY. Role of viral infection in sudden hearing loss. J Int Med Res. 2019;47(7):2865–72. DOI: 10.1177/0300060519847860
[28] Fancello V, Hatzopoulos S, Corazzi V, Bianchini C, Skarżyńska MB, Pelucchi S, et al. SARS-CoV-2 (COVID-19) and audio-vestibular disorders. Int J Immunopathol Pharmacol. 2021;35:20587384211027373. DOI: 10.1177/20587384211027373
[29] Magro CM, Mulvey J, Kubiak J, Mikhail S, Suster D, Crowson AN, et al. Severe COVID-19: A multifaceted viral vasculopathy syndrome. Ann Diagn Pathol. 2021;50:151645. DOI: 10.1016/j.anndiagpath.2020.151645
[30] Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):422. DOI: 10.1186/s13054-020-03120-0

[31] Marcink TC, Kicmal T, Armbruster E, Zhang Z, Zipursky G, Golub KL, et al. Intermediates in SARS-CoV-2 spike-mediated cell entry. Sci Adv. 2022;8(33):eabo3153. DOI: 10.1126/sciadv.abo3153
[32] Uranaka T, Kashio A, Ueha R, Sato T, Bing H, Ying G, et al. Expression of ACE2, TMPRSS2, and Furin in mouse ear tissue, and the implications for SARS-CoV-2 infection. Laryngoscope. 2021;131(6):E2013–E17. DOI: 10.1002/lary.29324
[33] Young A, Ng M. Otoacoustic emissions In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2024 [cited 2024 Apr 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/35593808/
[34] Salvi R, Sun W, Ding D, Chen GD, Lobarinas E, Wang J, et al. Inner hair cell loss disrupts hearing and cochlear function leading to sensory deprivation and enhanced central auditory gain. Front Neurosci. 2017;10:621. DOI: 10.3389/fnins.2016.00621
[35] Reynolds JL, Mahajan SD. SARS-CoV-2 alters blood-brain barrier integrity contributing to neuro-inflammation. J Neuroimmune Pharmacol. 2021;16(1):4–6. DOI: 10.1007/s11481-020-09975-y
[36] Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying mechanisms and assessment of an olfactory route to brain infection. Neuroscientist. 2021;27(6):582–3. DOI: 10.1177/1073858420956905
[37] Frazier KM, Hooper JE, Mostafa HH, Stewart CM. SARS-CoV-2 virus isolated from the mastoid and middle ear: Implications for COVID-19 precautions during ear surgery. JAMA Otolaryngol Head Neck Surg. 2020;146(10):964–66. DOI: 10.1001/jamaoto.2020.1922
[38] Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and antithrombotic treatment in coronavirus 2019: A new challenge. Thromb Haemost. 2020;120(6):949–56. DOI: 10.1055/s-0040-1710317
[39] Knight R, Walker V, Ip S, Cooper JA, Bolton T, Keene S, et al. Association of COVID-19 with major arterial and venous thrombotic diseases: A population-wide cohort study of 48 million adults in England and Wales. Circulation. 2022;146(12):892–6. DOI: 10.1161/CIRCULATIONAHA.122.060785
[40] De Luca P, Scarpa A, Ralli M, Tassone D, Simone M, De Campora L, et al. Auditory disturbances and SARS-CoV-2 infection: Brain inflammation or cochlear affection? Systematic review and discussion of potential pathogenesis. Front Neurol. 2021;12:707207. DOI: 10.3389/fneur.2021.707207
[41] Corazzi V, Migliorelli A, Bianchini C, Pelucchi S, Ciorba A. Hearing loss and blood coagulation disorders: A review. Hematol Rep. 2023;15(3):421–31. DOI: 10.3390/hematolrep15030043
[42] Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19. Am J Hematol. 2020;95(12):1578–89. DOI: 10.1002/ajh.25982
[43] Chern A, Famuyide AO, Moonis G, Lalwani AK. Bilateral sudden sensorineural hearing loss and intralabyrinthine hemorrhage in a patient with COVID-19. Otol Neurotol. 2021;42(1):e10–e14. DOI: 10.1097/MAO.0000000000002860
[44] Ciorba A, Corazzi V, Skarżyński PH, Skarżyńska MB, Bianchini C, Pelucchi S, Hatzopoulos S. Don't forget ototoxicity during the SARS-CoV-2 (Covid-19) pandemic!. Int J Immunopathol Pharmacol. 2020;34:2058738420941754. DOI: 10.1177/2058738420941754
[45] Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res. 2020;177:104762. DOI: 10.1016/j.antiviral.2020.104762
[46] Zoccali F, Cambria F, Colizza A, Ralli M, Greco A, de Vincentiis M, et al. Sudden sensorineural hearing loss after third dose booster of COVID-19 vaccine administration. Diagnostics (Basel). 2022;12(9):2039. DOI: 10.3390/diagnostics12092039
[47] Canales Medina M, Ramirez Gómez M. Tinnitus, sudden sensorineural hearing loss, and vestibular neuritis as complications of the Astra Zeneca COVID-19 vaccine. Cureus. 2022;14(1):e20906. DOI: 10.7759/cureus.20906
[48] Jeong J, Choi HS. Sudden sensorineural hearing loss after COVID-19 vaccination. Int J Infect Dis. 2021;113:341–43. DOI: 10.1016/j.ijid.2021.10.025

Сучасні патогенетичні аспекти втрати слуху при COVID: огляд літератури

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Анотація. За прогнозами Всесвітньої організації охорони здоров'я до 2050 року до 10 % населення планети потребуватимуть реабілітації для розв'язання проблеми інвалідизуючої втрати слуху. Метою цієї статті було з'ясувати основні механізми зниження слуху, пов'язаного з інфікуванням Severe Acute Respiratory Syndrome Coronavirus 2. Під час дослідження були опрацьовані сучасні англомовні наукові публікації переважно з високим індексом цитування через фахові платформи MEDLINE/PubMed та Index Medicus. Всього було обрано 48 джерел. Було проаналізовано статті присвячені розвитку кондуктивної або сенсоневральної приглухуватості, яка виникла безпосередньо внаслідок вірусного захворювання, або пов'язана з процесами, які його супроводжують (лікування, супутня патологія, вакцинація тощо). Встановлено, що розвиток вірусно-індукованої приглуховатості при COVID має мультифакторну природу. Гетерогенність аудіологічних змін насамперед обумовлена прямим вірусним пошкодженням клітин слухового аналізатора, які експресують мембранні рецептори ангіотензинперетворювального ферменту другого типу. Крім того, відбувається реактивація латентної вірусної інфекції, екстравазація ексудату в порожнину середнього вуха, порушення згортання крові, імуноопосередковане пошкодження клітин, місцева і генералізована запальна реакція, які впливають як на ланку звукопроведення, так і на звукосприйняття, як на одному вусі, так і на обох. Деякі випадки аудіологічних розладів можуть бути і ятрогенного походження, оскільки не виключені поствакцинальні ускладнення та ототоксичний вплив медикаментів, які використовуються у лікуванні COVID-19, що слід враховувати клініцистам на усіх рівнях медичної допомоги для ефективного менеджменту конкретного клінічного сценарію

Ключові слова: аудіологія; кондуктивна приглухуватість; сенсоневральна приглухуватість; коронавірус; ототоксичність; вакцинація