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PREGLED LITERATURE O KOVID-19 I AUDIO-VESTIBULOLOŠKIH SIMPTOMIMA: ŠTA ZNAMO DO SADA?

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SAŽETAK

Uvod/Cilj: Iako smo već ušli u treću godinu pandemije, patofiziološki mehanizmi infekcije korona virusom teškog akutnog respiratornog sindroma (SARS-CoV-2) i dalje nisu u potpunosti razjašnjeni. Simptomi čula mirisa i ukusa su povezivani sa ovom infekcijom od početka, ali do sada se nije puno govorilo o drugim senzornim sistemima, na prvom mestu čulu sluha i ravnoteže. Cilj ovoj revijalnog rada je da sumira podatke i najnovija saznanja iz literature i da pokuša da odgovori na pitanje da li postoji uzročna povezanost između COVID-19 i oštećenja unutrašnjeg uva.
Metode: U okviru ovog preglednog rada su prikazani najnoviji podaci i dokazi dobijeni na osnovu pretraživanja baze podataka *PubMed* korišćenjem odgovarajućih ključnih reči: *COVID-19*, *hearingloss*, *tinnitus* i *vertigo*. Prilikom pretrage identifikovano je preko 460 publikacija. Nakon pregleda naslova i apstrakata, većina radova su isključeni iz dalje analize jer nisu ispunili kriterijume sistematskog pregleda.
Rezultati: Ukupno 16 radova koji su ispunili zadate kriterijume pregledani su u celini. Rezultati meta-analize su ukazali na to da je stopa pojave oštećenja sluha 3,1% (Interval poverenja - IP: 0,01-0,09), zujanja u uvu 4,5% (IP: 0,012-0,153) i nesvestice 12,2% (IP: 0,070-0,204).
Zaključak: Većina publikovanih radova ima nedostataka i veliki rizik pristrasnosti (bez kontrolne grupe, sa dosta nedostajućih podataka i bez osvrta na pridružene faktore). Za sada još uvek nije moguće sa sigurnošću tvrditi da postoji uzročna povezanost između ove infekcije i oštećenja čula sluha i čula za ravnotežu.

Ključne reči: Covid-19, oštećenje sluha, SARS-CoV-2 virus, tinitus, vrtoglavica

Uvod

Svetska zdravstvena organizacija (SZO) je objavila pandemiju bolesti izazvane korona virusom (engl. *Coronavirus Disease* – COVID-19) 11. marta 2020. godine i u ovom trenutku u toku smo treće godine pandemije sa skoro 500 miliona zaraženih osoba i više od 6 miliona umrlih (1). U početku su samo respiratorni i gastrointestinalni simptomi bili dobro opisani, ali tokom prethodne dve godine mnoštvo drugih simptoma povezanih sa ovom infekcijom je prijavljeno u literaturi. Poremećaji čula mirisa i ukusa (hiposmija/anosmija i hipogeuzija/ageuzija) navedeni su kao karakteristični simptomi na početku pandemije i ostaju najčešće prijavljivani simptomi povezani sa uhom, grlom i nosem do sada.

Primećene su neurotropne karakteristike virusa, a do 30% pacijenata iskusi neurološke manifestacije ove bolesti (2,3). Ranije je dokazano da virusi mogu da dovedu do naglog, akutnog senzorineuralnog oštećenja sluha (eng. *Sudden SensoriNeural Hearing Loss* – SSNHL) ili akutne unilateralne periferne vestibulopatije (4,5). Predloženi mehanizmi uključuju direktno virusno oštećenje lavirinta ili nerva, reaktivaciju latentnog virusa, ili posredovani imuni mehanizam kod sistemske virusne infekcije (6,7). Desetak studija slučaja i serija slučajeva je publikovano u literaturi od početka pandemije ukazujući da virus SARS-CoV-2 takođe može da dovede do oštećenja sluha ili poremećaja ravnoteže preko nekoliko prethodno opisanih

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REVIEW OF COVID-19 AND AUDIO-VESTIBULAR SYMPTOMS: WHAT WE KNOW SO FAR?

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SUMMARY

Introduction/Aim: Although we have already entered the third year of the pandemic, the pathophysiological mechanisms of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infection are still not fully elucidated. While symptoms of smell and taste dysfunction have been associated with this infection from the beginning, not much has been reported on other sensory systems, in the first place the hearing and balance. The aim of this review paper is to summarize data from the literature and the latest publications and answer the question whether there is a causal link between COVID-19 and inner ear damage.
Methods: This review paper presents the latest data and evidence obtained from search of PubMed database by keywords: COVID-19, hearing loss, tinnitus and vertigo. The search identified more than 460 publications. After reviewing the title and abstract, most papers were excluded due to non-compliance with the eligibility criteria.
Results: A total of 16 papers fulfilled the eligibility criteria and were reviewed in their entirety. The results of the meta-analysis indicated that the incidence of hearing loss was 3.1% (Confidence Interval - CI: 0.01-0.09), of tinnitus 4.5% (CI: 0.012-0.153), and dizziness 12.2% (CI: 0.070-0.204).
Conclusion: Most published papers are characterized by limitations and high risk of bias (no control arm, missing data, and no reference to confounding factors). For now, no certain causal relationship between this infection and damage to the senses of hearing and the sense of balance can be established.

Key words: Covid-19. hearing loss, SARS-CoV-2, tinnitus, vertigo

Introduction

The pandemic of corona virus disease (COVID-19) was announced on 11 of March of 2020 by the World Health Organization (WHO) and at this point, we are into its third year, with almost 500 million infected individuals and over 6 million dead (1). In the beginning, only respiratory and gastrointestinal symptoms were well described, but during previous two years, a plethora of other symptoms connected with this infection were reported in the literature. A dysfunction of smell and taste (hyposmia/anosmia and hypogeusia/ageusia) were listed as hallmark symptoms early in the pandemic and remain most commonly reported ear, nose and throat symptoms up to date.

The neurotropic properties of the virus were observed and up to 30% of patients experience neurological manifestations of the disease (2,3). It has been shown previously that viruses can lead to sudden sensorineural hearing loss (SSNHL) or acute unilateral peripheral vestibulopathy (4,5). The proposed mechanisms include direct viral invasion of the labyrinth or nerve, reactivation of latent virus, or immune-mediated mechanism in systemic viral infection (6,7). A dozen of case reports and case series appeared in the literature from the beginning of pandemic suggesting that SARS-CoV-2 virus could also lead to hearing loss or balance disorders via several previously well described pathways: vascular, metabolic, autoimmune, or inflammatory (6). While it was of utmost importance to draw attention of the physicians to any new possible symptoms or organ damage in this disease, uncritical publishing, and

puteva: vaskularnog, metaboličkog, autoimunskog, ili inflamatornog (6). Dok je od najveće važnosti bilo skrenuti pažnju lekarima na nove moguće simptome ili oštećenja organa u ovoj bolesti, nekritičko objavljivanje i nedostatak pažljivog procesa stručne recenzije tokom pandemije doveli su do ozbiljnih pristrasnosti i netačnih povezanosti.

Do sada je objavljeno nekoliko sistematskih prikaza i dve meta-analiza o ovoj temi, ali zbog ozbiljnih nedostataka objavljene literature (nekontrolisane studije, nedostajući podaci, pristrasnost prisećanja, informativna pristrasnost i pridruženi faktori), veza između KOVID-19 oboljenja i oštećenja sluha ili vrtoglavice ostaje nesigurna. Takođe, većina objavljenih studija ne potvrđuje i ne prikazuje činjenice da je tokom pandemije većina pacijenata lečena ototoksičnim lekovima: hidroksihlorokin, azitromicin, i lopinavir-ritonavir, da nabrojimo samo nekoliko, koji bi sami po sebi mogli da budu uzrok oštećenja čula sluha i vestibularnog oštećenja (8). Da stvari budu još teže, od januara 2021. godine pojavio se jedan broj izveštaja o oštećenju sluha i nesvestici nakon jedne ili dve doze vakcine protiv KOVID-19. Iako su te informacije već dovedene u pitanje (9), reference za ove tvrdnje se i dalje mogu naći širom Interneta.

Cilj ovog rada bio je da se pretraži relevantna literatura i najnoviji rezultati i da se odgovori na pitanje da li imamo dovoljno dokaza da pretpostavimo uzročno-posledičnu vezu između KOVID-19 oboljenja i oštećenja sluha i vrtoglavice. Takođe, cilj je da se istaknu nedostaci u dostupnoj literaturi i rasvetle audio-vestibularni simptomi nakon vakcinacije.

Metode

Pretraživanje i pregled literature dostupne na engleskom jeziku putem *PubMed* baze podataka bilo je fokusirano na audiološke i vestibularne manifestacije Kovida-19. Ključne reči (MeSH termini) uključivale su sledeće: „COVID-19“, „hearing loss“, „tinnitus“ i „vertigo“. Poslednje pretraživanje literature je bilo 1. aprila 2022. Pretraživanje je iznedrilo 460 radova koji su filtrirani pregledom naslova i sažetaka, a zatim uz pomoć sledećih kriterijuma: (1) rad utvrđuje direktnu temporalnu vezu između novo dijagnostifikovanog oštećenja sluha i infekcije Kovidom-19 (do 4 nedelje), (2) infekcija se dokazuje testom lančane reakcije polimeraze (PCR) ili detekcijom specifičnih antitela uz pomoć serološkog testa (poželjno IgM) po preporukama (10) ili prijavom prijema u bolnicu zbog virusne pneumonije, (3) i drugi razlozi, koji mogu da izazovu senzorno oštećenje čula sluha, su isključeni ili barem navedeni. Od svih radova koji su prvobitno identifikovani, samo 16 radova je zadovoljilo sva tri gore navedena kriterijuma. Metodologija je bila u skladu sa preporučenim PRISMA protokolom (eng. P*referred Reporting Items for Systematic Reviews and Meta-analyses*) (11). Analizirane primarne studije su imale visok rizik od pristrasnosti (pristrasnost izveštavanja, informativna i druge vrste pristrasnosti).

Rezultati

Oštećenje sluha

Izolovani prikazi slučaja su pregledani i kratko razmotreni zbog ozbiljnih ograničenja u prikazivanju. Prvi rad o mogućoj vezi između oštećenja sluha i Kovida-19 je objavljen rano na početku pandemije, u maju 2020 (12). Rad je bio u formi preliminarnog prikaza, dok su mnogi važni detalji o pacijentima nedostajali (bez informacije o testovima, vremenske usklađenosti, pre ili post-audiograma ili mogućim pridruženim faktorima). Usledili su drugi prikazi slučaja, i većina njih je bila zasnovana na pojedinačnim izveštajima nedovoljnog kvaliteta, dok je samo nekoliko ispunilo sve preporučene kriterijume (13-17).

Bilo je drugih prikaza o uticaju Kovida-19, koji su poredili broj pacijenata sa SSNHL sa periodom pre pandemije (18). Iako je primećen ozbiljan pad apsolutnih brojeva pacijenata sa SSNHL, nije primećena promena u procentima pacijenata kod kojih je dijagnostikovan SSNHL u poređenju sa ukupnim brojem pregledanih pacijenata tokom dva perioda istraživanja, tako da nije pronađena veza između Kovida-19 i SSNHL-a.

U većini objavljenih studija o simptomima unutrašnjeg uva se, nažalost, javlja nedostatak odgovarajućih dijagnostičkih podataka i one se zasnivaju na subjektivnim merama koje su korišćene za procenu simptoma oštećenja sluha ili stepena nestabilnosti (19,20). Može se tvrditi da bi u toku visoko zarazne bolesti bilo teško i nepraktično koristiti standardnu opremu zbog teškoća u sanaciji i obzirima kliničkog okruženja. Međutim, bez audiometrije (početna vrednost, pre bolesti, i druga, nakon što je primećeno oštećenje sluha), nemo-

lack of careful peer review process during the pandemic also brought forth serious biases and spurious conjunctions.

Up to date, several systematic reviews and two meta-analyses were published on this topic, but due to serious limitations of the published literature (uncontrolled studies, missing data, recall and information bias, confounding factors, etc.) the association between COVID-19 and hearing loss or vertigo remains uncertain. Furthermore, most of the published studies fail to acknowledge and account to the fact that, during the pandemic, the majority of patients were treated with ototoxic drugs: hydroxychloroquine, azithromycin, and lopinavir-ritonavir, to name just a few, which could also be cause of hearing loss and vestibular dysfunction on their own (8). To aggravate matters further, since January 2021, a number of reports emerged on hearing loss and dizziness after one or two doses of COVID-19 vaccines. Although already questioned, the references to these claims can still be found online (9).

The aim of this paper was to search relevant literature and the latest findings and to answer the question whether we have enough proofs to assume causal association between COVID-19 and hearing impairment and vertigo. Moreover, it will point out the deficiencies in the available literature and hopefully shed a light on post-vaccination audio-vestibular symptoms.

Methods

The search and review of the literature available in English language was performed using PubMed database, with a focus on audiological and vestibular manifestations of COVID-19. The key words (MeSH terms) used were: "COVID-19", "hearing loss", "tinnitus" and "vertigo". The last literature search was performed on April 1, 2022. The search yielded 460 papers which were filtered by screening of title and abstract, and then using the following criteria: (1) the paper establishes a direct temporal link between newly diagnosed hearing loss and COVID-19 infection (up to 4 weeks), (2) the infection was proven by Polymerase Chain Reaction (PCR) test or detection of specific antibodies by serology (preferably IgM) as recommended (10) or report of a hospital admission due to viral pneumonia, (3) and other reasons that can cause a sensory deficit in hearing are ruled out or at least acknowledged. Of all paper initially identified, only 16 fulfilled all three criteria mentioned above. The recommended PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) were followed as recommended (11). The discussed primary studies had high risks of bias (reporting bias, information bias, and other types of bias).

Results

Hearing loss

Isolated case reports were screened and only briefly referred to due to severe deficiencies in the reporting. The first ever paper on possible connection between hearing loss and COVID-19 was published relatively early in the pandemic, in May 2020 (12). It was in a form of a preliminary report, with many important patients' details lacking (no information on tests, temporal concordance, pre- or post-audiological data, or possible confounding factors). Other case reports followed, and the vast majority of them were anecdotal and of insufficient quality, with only several of them fulfilling all the recommended criteria (13-17).

There are other reports on impact of COVID-19 which compared total numbers of patients with SSNHL with the pre-pandemic period (18). Although serious decline in absolute number of patients who presented with SSNHL was observed, no change in percentages of patients diagnosed with SSNHL compared to the total number of examined patients was observed in the two examined periods, so no association between COVID-19 and SSNHL could be found.

Most of the published studies on inner ear symptoms unfortunately lack the proper diagnostics data and are based only on subjective measures used to assess the symptoms of hearing loss or degree of instability (19,20). It could be argued that in times of highly infectious disease, it would be hard and impractical to use standardized equipment due to difficulties in sanitation and clinical environment concerns. But without audiometry (baseline reference, pre-disease, and second, after hearing loss was noticed) it is impossible to make the diagnosis of SSNHL (≥30 dB on three contiguous frequencies in 72 h) (6). Furthermore, making the diagnosis of hearing loss

guće je postaviti dijagnozu SSNHL (>30 dB na tri uzastopne frekvencije tokom 72h) (6). Takođe, postavljanje dijagnoze oštećenja sluha koja se zasniva samo na subjektivno prijavljenim merama ili upitnicima nije čvrsto naučno utemeljeno i dokazano je, ne samo da audiometrijski pragovi nisu u korelaciji sa subjektivno prijavljenim stepenom oštećenja sluha (21), već da subjektivno oštećenje sluha zavisi od stepena neuroticizma i sposobnosti pojedinaca da se izbore (22).

U jedinoj meta-analizi koja je objavljena do sada, prijavljena stopa pojave (eng. *event rate* – ER, pojavna učestalost događaja) oštećenja sluha bila je 3,1% (Interval povrenja - IP: 0,01-0,09) na osnovu ukupnog broja pacijenata koji je iznosio 560 (23). Ovu stopu pojave bi trebalo interpretirati uz oprez zbog niskog nivoa dokaza u primarnim studijama i velike heterogenosti.

Zujanje u uvu - tinitus

Ukupno 90 objavljenih radova opisuje tinitus ili kao prateći simptom tokom infekcije ili retko, kao izolovan simptom. Ne postoje studije koje prijavljuju psihometrijsku evaluaciju zujanja u ušima, ili njegovo trajanje, simptom skor i uticaj; samo u jednom radu je upoređena frekvencija i intenzitet (24). Prijavljena zbirna procenjena prevalencija tinitusa nakon infekcije Kovidom-19 je 8% (IP: 5 do 13%), a ER je 4,5% (IP: 0,012-0,153) (22-24). Treba navesti da emocionalni faktori, poput anksioznosti, straha, stresa i lošeg kvaliteta sna tokom pandemije takođe mogu da igraju važnu ulogu u percepciji i pogoršanju tinitusa, pogotovo kod osoba koje su bile u karantinu (25).

Vrtoglavica

Vrtoglavica je opšti termin i medicinska dijagnoza i obično označava iskustvo rotacione senzacije i kretanja zbog nistagmusa. S druge strane, kada govorimo o nesvestici (eng. *dizziness*), obično se to odnosi na osećaj gubitka svesti, osećaj lakoće u glavi, osećaj slabosti, ili nestabilnosti. Nažalost, zbog nedostatka jedinstvenog sistema klasifikacije, ova dva različita termina se često koriste naizmenično u literaturi, bez pravljenja razlike. U većini objavljenih studija o subjektivnim prikazima simptoma tokom Kovida-19, autori prijavljuju osećaj nesvestice, a ne vrtoglavice. Pored toga, evidentan je visok rizik pristrasnosti izveštavanja, kao i nedostajući podaci; samo jedna studija je opisala jednog pacijenta sa kompletnim objektivnim vestibularnim testiranjem i opisom nistagmusa (26). U jednom objavljenom sistematskom prikazu i meta-analizi, stopa pojave (ER) nesvestice bila je 12,2% (IP: 0,070-0,204) (23), dok je zbirna procena prevalencije rotatorne vrtoglavice bila mnogo niža 3,4% (IP: 1,1-6,9), kao što je i bilo očekivano (27).

Veza između simptoma unutrašnjeg uha i vakcinacije protiv KOVID-19

Nekoliko anegdotalnih prikaza slučaja zasnovanih na pojedinačnim izveštajima se pojavilo u literaturi o SSNHL nakon vakcinacije protiv Kovida-19. Preporučeni dijagnostički kriterijumi ili nisu bili praćeni ili nisu prikazani u objavljenim radovima, tako da ozbiljnost slučajeva nije mogla biti utvrđena. U jednoj studiji preseka koja je uključila ukupno 555 izveštaja o verovatnom SSNHL u okviru Sistema za prijavljivanje neželjenih efekata vakcine (engl. V*accine Adverse Events Reporting System* – VAERS) Centra za prevenciju i kontrolu bolesti Sjedinjenih Američkih Država, rezultati nisu ukazali na vezu između vakcinacije protiv KOVID-19 i povećane incidencije oštećenja sluha u poređenju sa očekivanom incidencijom u opštoj populaciji (9).

Diskusija

Oštećenje audio-vestibularnog sistema u Kovid-19 infekciji ostaje mogućnost. Oštećenje osetljivih struktura unutrašnjeg uha može se povezati sa direktnim uticajem virusa, ali se takođe može dovesti u vezu sa posredovanim imunskim odgovorom. Krvni sudovi, limfni sistem, nervi i u nekim slučajevima meninge, predloženi su kao putevi ulaska virusa (14,19). Tačna anamneza i objektivno testiranje ključni su za pravilnu identifikaciju oštećenja i moguću etiopatogenezu. Druge mogućnosti i potvrđeni slučajevi oštećenja unutrašnjeg uha moraju biti isključeni pre postavljanja konačne dijagnoze ili bilo kakvih tvrdnji o uzročnoj vezi. Naime, kod svih Kovid-19 pacijenata bi trebalo istražiti i isključiti prethodnu istoriju izloženosti buci, traume glave, autoimune bolesti, i druge bolesti unutrašnjeg uva, poput Menierove bolesti. Takođe je postavljena hipoteza da sinergijski audio-vestibularni neželjeni efekti mogu da se jave kod primene mnogih ototoksičnih Kovid-19 lekova (hidroksihlorokin, azitromicin, lopinavir-ritonavir, remdesivir, favipiravir, furosemid, itd.) (8). Drugi faktori, kao što su starija životna dob, neprepoznato oštećenje čula sluha, genetska predispozicija i smanjena eliminacija lekova mogu takođe odi-

based only on subjective reported measures or questionnaires is not scientifically sound and has been proven not only that audiometric thresholds do not correlate well with subjective reported hearing level (21), but also that subjective hearing disability depends on the degree of neuroticism and coping expectancy of the individuals (22).

In the only one meta-analysis published so far, the reported event rate (ER, the occurrence frequency of the event) in case of hearing loss was 3,1% (CI: 0.01-0.09) based on total population of 560 patients (23). This ER should be interpreted with caution due to low level of evidence in primary studies and high heterogeneity.

Tinnitus

A total of 90 published papers are describing tinnitus either as concomitant symptom during the infection or rarely, as isolated one. There are no studies which report psychometric evaluation of the tinnitus, or its duration, resolution of symptom and impact; only one reported its matching frequency and intensity (24). The reported pooled estimated prevalence of tinnitus after COVID-19 infection is 8% (CI: 5 to 13%) and ER is 4.5% (CI: 0.012-0.153) (23-25). It should be noted that other emotional factors, such anxiety, fear, stress, and poor sleep quality during the pandemic can also play a significant role in perceiving and aggravation of tinnitus, especially in persons who were quarantined (25).

Vertigo

Vertigo is a general term and medical diagnosis and usually implies experiencing rotatory sensation and movement due to nystagmus. On the other hand, when we talk about dizziness, we usually refer to feeling faint, light-headed, weak, or unsteady. Unfortunately, due to lack of uniform classification systems, these two different terms are commonly used interchangeably in literature. In most of the published studies with subjective reports on symptoms experienced during COVID-19, authors report the feeling of dizziness, not vertigo. Furthermore, the high risk of reporting bias and missing data is evident; only one study described one patient with complete objective vestibular testing and description of nystagmus (26). In published systematic review and meta-analysis, ER of dizziness was reported to be 12.2% (CI: 0.070-0.204) (23), while pooled estimate of the prevalence of rotatory vertigo (without dizziness) was much lower 3,4% (CI: 1,1-6,9), as expected (27).

Association of inner ear symptoms and COVID-19 vaccination

Several anecdotal case reports have also occurred in literature on SSNHL after COVID-19 vaccination. The recommended diagnostic criteria for SSNHL were either not followed or not reported in the published papers, so the severity of cases could not be established. In the cross-sectional study of all 555 incident reports of probable SSNHL in the Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System (VAERS), findings did not suggest an association between COVID-19 vaccination and increased incidence of hearing loss compared with the expected incidence in the general population (9).

Discussion

The damage of audio-vestibular system in COVID-19 infection remains a possibility. While damage of the sensitive inner ear structures can be related to direct effect of the virus, it could also be related to the virus-mediated immune response. Blood vessels, lymphatics, nerves and in some cases, meninges have all been proposed as entry routes for the virus (14,19). An accurate anamnesis and objective testing are crucial for correct identification of damage and possible etiopathogenesis. Other possibilities and confirmed causes of inner ear damage must be ruled out before making the final diagnosis or any claims of causal relationship. Namely, previous history of noise exposure, head trauma, autoimmune diseases, and other inner ear diseases such as Meniere disease should always be actively searched for and ruled out in all COVID-19 patients. It has also been postulated that synergistic adverse audio-vestibular effects may occur with coadministration of multiple ototoxic COVID-19 drugs (hydroxychloroquine, azithromycin, lopinavir-ritonavir, remdesivir, favipiravir, furosemide, etc.) (8). Other factors, such as old age, unrecognized hearing impairment, genetic susceptibility and reduced drug elimination can also play significant role in the inner ear damage. Unfortunately, this is not acknowledged in most of the published studies to date.

The uncritical and mass publishing from the beginning of the pandemic has led to hundreds

grati važnu ulogu u oštećenju unutrašnjeg uva. Nažalost, to nije potvrđeno u većini studija koje su do danas objavljene.

Nekritičko i masovno objavljivanje od početka pandemije dovelo je do objavljivanja na stotine studija lošeg kvaliteta izveštavanja. Kvalitet skoro svih ocenjenih studija u ovom rukopisu smatra se slabim, zbog nekontrolisanog dizajna i sklonosti ka pristrasnosti informacija i selekcije, grešaka merenja i pridruženih faktora. U drugoj godini pandemije, mnogi objavljeni radovi su unapredili kvalitet prikazanih dokaza, a potpuni audiometrijski podaci, vestibularno testiranje i neuro snimanje su bili dostupni. Osim ovih prikaza slučaja, studija preseka sa jednom grupom i kohortnih studija, do sada su objavljena četiri sistematska pregleda i dve meta-analize o ovoj temi (23,25,27-29). Međutim, zbog velike heterogenosti podataka, visokog rizika pristrasnosti u primarnim studijama i faktora zabune, rezultate svih ovih studija bi trebalo interpretirati uz oprez. U jednoj od meta-analiza koje su primenjivale konzervativnije kriterijume, procene zbirne prevalencije i intervali poverenja za oštećenje sluha, zujanje u ušima i vrtoglavicu bili su 3,86% (95% IP: 0,84-8,42), 9,62% (95% IP: 3,60-18,13), i 2,4% (95% IP: 0,47-6,01) (29). Iako su procene revidirane i stope su pale za skoro 50% za oštećenje sluha i vrtoglavicu i više od 98% uključenih pacijenata je imalo pozitivan PCR test, autori i dalje insistiraju na oprezu prilikom tumačenja podataka. I dalje postoji puno faktora koji mogu da igraju ulogu u patofiziologiji oštećenja unutrašnjeg uha, a koji nisu mogli biti kontrolisani.

Autori nedavno objavljene studije su pokušali da razjasne da li postoji prava veza između Kovida-19 i auditornih simptoma poredeći ih sa drugim tipovima simptoma: oni sa dokazanom vezom sa Kovidom-19 (gubitak čula mirisa i ukusa) i oni koji nemaju utvrđenu vezu (zubobolja) (30). S obzirom da je više od 60% učesnika sa potvrđenim ili verovatnim Kovidom-19, osim simptoma unutrašnjeg uha, prijavilo da je bolest uticala na zubobolju, autor nije mogao odrediti da li su ovi simptomi zaista povezani sa Kovidom-19 ili odražavaju nocebo efekat (novi ili pogoršanje postojećih simptoma koji se razvijaju zbog negativnih informacija ili uverenja povezanih sa zdravljem). Oni su takođe postavili hipotezu da to može biti zbog mogućnosti da su učesnici bili visoko osetljivi na somatske senzacije ili zbog zdravstvene anksioznosti (31).

Zaključak

U ovom preglednom radu je detaljno ispitano šesnaest studija. Objavljeni sistematski pregledi i meta-analize su pokazali da je prevalencija oštećenja sluha, zujanja u ušima i nesvestice značajno viša kod pacijenata sa Kovidom-19. Međutim, imajući u vidu loš kvalitet primarnih studija i visok rizik od pristrasnosti, ove nalaze bi treba interpretirati uz oprez. Na osnovu dostupnih dokaza, i dalje nije moguće ustanoviti uzročnu vezu između Kovida-19 i oštećenja unutrašnjeg uha. Potrebno je više studija dobrog dizajna i dodatnih procena sa standardnim objektivnim testovima da bi se u potpunosti razjasnila incidencija i ozbiljnost simptoma unutrašnjeg uha kod Kovid-19 bolesti.

Konflikt interesa

Autor je izjavio da nema konflikta interesa.

Literatura

1. World Health Organization. Coronavirus (COVID-19) Dashboard Overview. (Last assessed April 8, 2022); Available at: https://covid19.who.int/
2. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021; 24(2):168-175. doi: 10.1038/s41593-020-00758-5
3. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 2020; 77:8-12. (doi: 10.1016/j.jocn.2020.05.017)
4. Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. Trends Hear 2014; 18:2331216514541361. doi: 10.1177/2331216514541361
5. Hegemann SCA, Wenzel A. Diagnosis and Treatment of Vestibular Neuritis/Neuronitis or Peripheral Vestibulopathy (PVP)? Open Questions and Possible Answers. Otol Neurotol 2017; 38(5):626-631. doi: 10.1097/MAO.0000000000001396
6. 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(1_suppl):S1-S45. doi: 10.1177/0194599819859885
7. Merchant SN, Durand ML, Adams JC. Sudden deafness: is it viral? ORL J OtorhinolaryngolRelat Spec 2008; 70(1):52-60; discussion 60-2. doi: 10.1159/000111048
8. Little C, Cosetti MK. A Narrative Review of Pharmacologic Treatments for COVID-19: Safety Considerations and Ototoxicity. Laryngoscope 2021; 131(7):1626-1632. doi: 10.1002/lary.29424
9. Formeister EJ, Wu MJ, Chari DA, Meek R 3rd, Rauch SD, Remenschneider AK, et al. Assessment of Sudden

of published studies with poor reporting quality. The quality of almost all assessed studies in this manuscript were regarded as weak because of uncontrolled design and proneness to selection and information bias, measurement errors and confounding factors. In the second year of pandemic, many published papers improved the quality of reported evidence, and full audiometry data, vestibular testing and neuroimaging was available. Apart from case reports, single-arm cross-sectional and cohort studies, up to date four systematic reviews and two meta-analyses were also published on this subject (23,25,27-29). However, due to high heterogeneity of the data, high risk of bias in primary studies and confounding factors, results of all these studies should be interpreted with caution. In one of the meta-analyses which applied more conservative criteria, pooled prevalence estimates and confidence intervals for hearing loss, tinnitus and vertigo were 3.68% (95% CI: 0.84 – 8.42), 9.62% (95% CI: 3.60 – 18.13), and 2.4% (95% CI: 0.47 – 6.01), respectively (29). Although the estimate was revised and rates fell for almost 50% for hearing loss and vertigo and more than 98% of included patients had positive PCR test, authors still urge caution in interpreting the data. There are still many contributing uncontrolled factors that can still play a role in pathophysiology of inner ear damage.

The authors of recently published study tried to elucidate if there is true association between COVID-19 and auditory symptoms by comparing them with other types of symptoms: those with proven association with COVID-19 (loss of smell and taste) and those with no established association(toothache) (30). Since over 60% of participants with confirmed or probable COVID-19, apart from inner ear symptoms, reported that their toothache had also been affected by the disease, the authors could not determine whether these symptoms are indeed associated with COVID-19 or they reflect nocebo effect (new or worsening of the existing symptoms that develop due to negative health/related information or belief). They also postulated that it could be due to a possibility that participants were highly sensitive to somatic sensations or health anxiety (31).

Conclusion

This review examined sixteen studies in detail. Published systematic reviews and meta-analyses have demonstrated that the prevalence of hearing loss, tinnitus and dizziness is significantly higher in patients with COVID-19. However, given the poor quality of primary studies and high risk of bias, these findings should be interpreted with caution. Based on the available evidence, it is still not possible to ascertain the casual relationship between COVID-19 and inner ear damage. More well-designed studies and follow-up assessments with standard objective tests are needed to fully elucidate incidence and severity of inner ear symptoms in COVID-19 disease.

Competing interests

The author declares no competing interests.

Literature

1. World Health Organization. Coronavirus (COVID-19) Dashboard Overview. (Last assessed April 8, 2022); Available at: https://covid19.who.int/
2. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021; 24(2):168-175. (doi: 10.1038/s41593-020-00758-5
3. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci 2020; 77:8-12. doi: 10.1016/j.jocn.2020.05.017)
4. Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. Trends Hear 2014; 18:2331216514541361. doi: 10.1177/2331216514541361
5. Hegemann SCA, Wenzel A. Diagnosis and Treatment of Vestibular Neuritis/Neuronitis or Peripheral Vestibulopathy (PVP)? Open Questions and Possible Answers. Otol Neurotol 2017; 38(5):626-631. doi: 10.1097/MAO.0000000000001396
6. 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(1_suppl):S1-S45. doi: 10.1177/0194599819859885
7. Merchant SN, Durand ML, Adams JC. Sudden deafness: is it viral? ORL J OtorhinolaryngolRelat Spec 2008; 70(1):52-60; discussion 60-2. doi: 10.1159/000111048
8. Little C, Cosetti MK. A Narrative Review of Pharmacologic Treatments for COVID-19: Safety Considerations and Ototoxicity. Laryngoscope 2021; 131(7):1626-1632. (doi: 10.1002/lary.29424

Sensorineural Hearing Loss After COVID-19 Vaccination. JAMA Otolaryngol Head Neck Surg 2022: e214414. doi: 10.1001/jamaoto.2021.4414

10. Popadic D. PCR testing for SARS-CoV-2: Practice, recommendations, and dilemmas. Health Care 2020; 49(3):56-74. doi: 10.5937/zdravzast49-28696
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62(10):1006-12. doi: 10.1016/j.jclinepi.2009.06.005
12. 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
13. Koumpa FS, Forde CT, Manjaly JG. Sudden irreversible hearing loss post COVID-19. BMJ Case Rep 2020; 13(11):e238419. doi: 10.1136/bcr-2020-238419
14. Degen C, Lenarz T, Willenborg K. Acute Profound Sensorineural Hearing Loss After COVID-19 Pneumonia. Mayo Clin Proc 2020; 95(8):1801-1803. doi: 10.1016/j.mayocp.2020.05.034
15. 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
16. Edwards M, Muzaffar J, Naik P, Coulson C. Catastrophic bilateral sudden sensorineural hearing loss following COVID-19. BMJ Case Rep 2021; 14(6):e243157. doi: 10.1136/bcr-2021-243157
17. Ricciardiello F, Pisani D, Viola P, Cristiano E, Scarpa A, Giannone A, et al. Sudden Sensorineural Hearing Loss in Mild COVID-19: Case Series and Analysis of the Literature. Audiol Res 2021; 11(3):313-326. doi: 10.3390/audiolres11030029
18. Chari DA, Parikh A, Kozin ED, Reed M, Jung DH. Impact of COVID-19 on Presentation of Sudden Sensorineural Hearing Loss at a Single Institution. Otolaryngol Head Neck Surg 2021; 165(1):163-165. doi: 10.1177/0194599820974685
19. 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 ImmunopatholPharmacol 2021; 35:20587384211027373. doi: 10.1177/20587384211027373
20. Almishaal AA, Alrushaidan AA. Short- and Long-Term Self-Reported Audiovestibular Symptoms of SARS-CoV-2 Infection in Hospitalized and Nonhospitalized Patients. AudiolNeurootol 2022; 1-15. doi: 10.1159/000521963
21. Korsten-Meijer AG, Wit HP, Albers FW. Evaluation of the relation between audiometric and psychometric measures of hearing after tympanoplasty. Eur Arch Otorhinolaryngol 2006; 263(3):256-62. doi: 10.1007/s00405-005-0983-5
22. Nordvik Ø, Heggdal POL, Brännström KJ, Aarstad AK, Aarstad HJ. Importance of personality and coping expectancy on patient-reported hearing disability, quality of lifeand distress level: a study of patients referred to an audiology service. Health Qual Life Outcomes 2021; 19(1):168.
23. Jafari Z, Kolb BE, Mohajerani MH. Hearing Loss, Tinnitus, and Dizziness in COVID-19: A Systematic Review and Meta-Analysis. Can J Neurol Sci 2022; 49(2):184-195. doi: 10.1017/cjn.2021.63
24. Chirakkal P, Al Hail AN, Zada N, Vijayakumar DS. COVID-19 and Tinnitus. Ear Nose Throat J 2021;100(2_suppl): 160S-162S. doi: 10.1177/0145561320974849
25. Beukes E, Ulep AJ, Eubank T, Manchaiah V. The Impact of COVID-19 and the Pandemic on Tinnitus: A Systematic Review. J Clin Med 2021; 10(13):2763. (doi: 10.3390/jcm10132763).
26. Mat Q, Noël A, Loiselet L, Tainmont S, Chiesa-Estomba CM, Lechien JR, Duterme JP. Vestibular Neuritis as Clinical Presentation of COVID-19. Ear Nose Throat J 2021:145561321995021. doi: 10.1177/0145561321995021
27. Almufarrij I, Munro KJ. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. Int J Audiol 2021; 60(12):935-945. doi: 10.1080/14992027.2021.1896793
28. Almufarrij I, Uus K, Munro KJ. Does coronavirus affect the audio-vestibular system? A rapid systematic review. Int J Audiol 2020; 59(7):487-491. doi: 10.1080/14992027.2020.1776406
29. Lough M, Almufarrij I, Whiston H, Munro KJ. Revised meta-analysis and pooled estimate of audio-vestibular symptoms associated with COVID-19. Int J Audiol 2021: 1-5. doi: 10.1080/14992027.2021.1962552
30. Saunders GH, Beukes E, Uus K, Armitage CJ, Kelly J, Munro KJ. Shedding Light on SARS-CoV-2, COVID-19, COVID-19 Vaccination, and Auditory Symptoms: Causality or Spurious Conjunction? Front Public Health 2022; 10:837513. doi: 10.3389/fpubh.2022.837513
31. Marcus DK, Gurley JR, Marchi MM, Bauer C. Cognitive and perceptual variables in hypochondriasis and health anxiety: a systematic review. Clin Psychol Rev 2007; 27(2):127-39. doi: 10.1016/j.cpr.2006.09.003

9. Formeister EJ, Wu MJ, Chari DA, Meek R 3rd, Rauch SD, Remenschneider AK, et al. Assessment of Sudden Sensorineural Hearing Loss After COVID-19 Vaccination. JAMA Otolaryngol Head Neck Surg 2022: e214414. doi: 10.1001/jamaoto.2021.4414
10. Popadic D. PCR testing for SARS-CoV-2: Practice, recommendations, and dilemmas. Health Care 2020; 49(3):56-74. (doi: 10.5937/zdravzast49-28696)
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62(10):1006-12. doi: 10.1016/j.jclinepi.2009.06.005
12. 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
13. Koumpa FS, Forde CT, Manjaly JG. Sudden irreversible hearing loss post COVID-19. BMJ Case Rep 2020;13(11):e238419. doi: 10.1136/bcr-2020-238419
14. Degen C, Lenarz T, Willenborg K. Acute Profound Sensorineural Hearing Loss After COVID-19 Pneumonia. Mayo Clin Proc 2020; 95(8):1801-1803. doi: 10.1016/j.mayocp.2020.05.034
15. 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
16. Edwards M, Muzaffar J, Naik P, Coulson C. Catastrophic bilateral sudden sensorineural hearing loss following COVID-19. BMJ Case Rep 2021; 14(6):e243157. doi: 10.1136/bcr-2021-243157
17. Ricciardiello F, Pisani D, Viola P, Cristiano E, Scarpa A, Giannone A, et al. Sudden Sensorineural Hearing Loss in Mild COVID-19: Case Series and Analysis of the Literature. Audiol Res 2021; 11(3):313-326. doi: 10.3390/audiolres11030029
18. Chari DA, Parikh A, Kozin ED, Reed M, Jung DH. Impact of COVID-19 on Presentation of Sudden Sensorineural Hearing Loss at a Single Institution. Otolaryngol Head Neck Surg 2021; 165(1):163-165. doi: 10.1177/0194599820974685
19. 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 ImmunopatholPharmacol 2021;35:20587384211027373. doi: 10.1177/20587384211027373
20. Almishaal AA, Alrushaidan AA. Short- and Long-Term Self-Reported Audiovestibular Symptoms of SARS-CoV-2 Infection in Hospitalized and Nonhospitalized Patients. AudiolNeurootol 2022: 1-15. doi: 10.1159/000521963
21. Korsten-Meijer AG, Wit HP, Albers FW. Evaluation of the relation between audiometric and psychometric measures of hearing after tympanoplasty. Eur Arch Otorhinolaryngol 2006; 263(3):256-62. doi: 10.1007/s00405-005-0983-5
22. Nordvik Ø, Heggdal POL, Brännström KJ, Aarstad AK, Aarstad HJ. Importance of personality and coping expectancy on patient-reported hearing disability, quality of lifeand distress level: a study of patients referred to an audiology service. Health Qual Life Outcomes 2021; 19(1):168.
23. Jafari Z, Kolb BE, Mohajerani MH. Hearing Loss, Tinnitus, and Dizziness in COVID-19: A Systematic Review and Meta-Analysis. Can J Neurol Sci 2022; 49(2):184-195. doi: 10.1017/cjn.2021.63
24. Chirakkal P, Al Hail AN, Zada N, Vijayakumar DS. COVID-19 and Tinnitus. Ear Nose Throat J 2021;100(2_suppl): 160S-162S. doi: 10.1177/0145561320974849
25. Beukes E, Ulep AJ, Eubank T, Manchaiah V. The Impact of COVID-19 and the Pandemic on Tinnitus: A Systematic Review. J Clin Med 2021; 10(13):2763. doi: 10.3390/jcm10132763
26. Mat Q, Noël A, Loiselet L, Tainmont S, Chiesa-Estomba CM, Lechien JR, Duterme JP. Vestibular Neuritis as Clinical Presentation of COVID-19. Ear Nose Throat J 2021:145561321995021. doi: 10.1177/0145561321995021
27. Almufarrij I, Munro KJ. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. Int J Audiol 2021; 60(12):935-945. doi: 10.1080/14992027.2021.1896793
28. Almufarrij I, Uus K, Munro KJ. Does coronavirus affect the audio-vestibular system? A rapid systematic review. Int J Audiol 2020; 59(7):487-491. doi: 10.1080/14992027.2020.1776406
29. Lough M, Almufarrij I, Whiston H, Munro KJ. Revised meta-analysis and pooled estimate of audio-vestibular symptoms associated with COVID-19. Int J Audiol 2021: 1-5. doi: 10.1080/14992027.2021.1962552
30. Saunders GH, Beukes E, Uus K, Armitage CJ, Kelly J, Munro KJ. Shedding Light on SARS-CoV-2, COVID-19, COVID-19 Vaccination, and Auditory Symptoms: Causality or Spurious Conjunction? Front Public Health 2022; 10:837513. doi: 10.3389/fpubh.2022.837513
31. Marcus DK, Gurley JR, Marchi MM, Bauer C. Cognitive and perceptual variables in hypochondriasis and health anxiety: a systematic review. Clin Psychol Rev 2007; 27(2):127-39. doi: 10.1016/j.cpr.2006.09.003

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