Does coronavirus affect the audio-vestibular system? A rapid systematic review

Ibrahim Almufarrij, Kai Uus & Kevin J. Munro

To cite this article: Ibrahim Almufarrij, Kai Uus & Kevin J. Munro (2020): Does coronavirus affect the audio-vestibular system? A rapid systematic review, International Journal of Audiology, DOI: 10.1080/14992027.2020.1776406

To link to this article: https://doi.org/10.1080/14992027.2020.1776406
Does coronavirus affect the audio-vestibular system? A rapid systematic review

Ibrahim Almufarrij\textsuperscript{a,b}, Kai Uusa\textsuperscript{a} and Kevin J. Munro\textsuperscript{a,c}

\textsuperscript{a}Manchester Centre for Audiology and Deafness, School of Health Sciences, University of Manchester, Manchester, UK; \textsuperscript{b}Department of Rehabilitation Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia; \textsuperscript{c}Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

\textbf{ABSTRACT}

\textbf{Objective:} This rapid systematic review investigated audio-vestibular symptoms associated with coronavirus.

\textbf{Design:} The protocol for the rapid review was registered in the International Prospective Register of Systematic Reviews and the review methods were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Risk of bias was assessed using the National Institute of Health quality assessment tools.

\textbf{Study sample:} After rejecting more than 2300 records, there were five case reports and two cross-sectional studies that met the inclusion criteria.

\textbf{Results:} No records of audio-vestibular symptoms were reported with the earlier types of coronavirus (i.e. severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]). Reports of hearing loss, tinnitus, and vertigo have rarely been reported in individuals who tested positive for the SARS-CoV-2.

\textbf{Conclusion:} Reports of audio-vestibular symptoms in confirmed COVID-19 cases are few, with mostly minor symptoms, and the studies are of poor quality. Emphasis over time is likely to shift from life-threatening concerns to longer-term health-related consequences such as audio-vestibular dysfunction. High-quality studies are needed to investigate the acute effects of COVID-19, as well as for understanding long-term risks, on the audio-vestibular system.

\textbf{Review registration:} Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020184932)

\textbf{ARTICLE HISTORY}

Received 15 May 2020
Revised 27 May 2020
Accepted 27 May 2020

\textbf{KEYWORDS}

Hearing loss; coronavirus; COVID-19; SARS-CoV2; tinnitus; vertigo

\textbf{Introduction}

In December 2019, several pneumonia cases with an unidentified aetiology were reported in Wuhan, China, and announced to the World Health Organisation (WHO 2020a). A novel coronavirus was identified on 6 January 2020 as the cause of these cases (also called severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). On 30 January 2020, WHO declared the novel coronavirus outbreak to be a global health emergency of international concern (WHO 2020b), whereupon the organisation renamed the novel coronavirus as Coronavirus Disease 2019 (COVID-19; WHO 2020b).

Within a matter of weeks, COVID-19 spread to over 200 countries, areas and territories (WHO 2020c). As of 14 May 2020, the total number of confirmed cases had surged to 4.25 million, with more than 294,000 deaths (WHO 2020c). There are a wide range of clinical features ranging from no symptoms to fever, dry cough, fatigue, shortness of breath, anosmia (i.e. loss of the sense of smell) and ageusia (i.e. loss of taste; Iacobucci 2020; Menni et al. 2020; Xu et al. 2020). A significant number of central and peripheral nervous system manifestations have been reported including cerebrovascular disease, impaired consciousness and impaired vision; however, it is unclear if these are a complication of COVID-19 or side effects of medication (Mao et al. 2020).

It is well known that some viral infections may cause hearing loss (Young 2020). For instance, sequelae of cytomegalovirus, rubella and measles can be sensorineural hearing loss (Cohen, Durstenfeld, and Roehm 2014). Studies on coronaviruses have shown sequelae to have neurotrophic and neuro-invasive characteristics (Sahin et al. 2020). Since coronavirus can cause peripheral neuropathy, including sensory neuropathy, one could hypothesise that COVID-19 has the potential to cause auditory neuropathy spectrum disorder (ANSD), a hearing disorder where the outer hair cells in the cochlea are functioning but transmission along the ascending neural pathway is impaired (Kim et al. 2017; Tsai et al. 2004). COVID-19 is reportedly associated with Guillain Barre Syndrome (GBS), an acute immune-mediated disease with central and peripheral nerves manifestations caused by various infections (Sedaghat and Karimi 2020). ANSD has been found to be associated with acquired neuropathies including GBS (Wong 1997).

\textbf{CONTACT} Ibrahim Almufarrij ialmufarrij@ksu.edu.sa  Manchester Centre for Audiology and Deafness, University of Manchester, Manchester M13 9PL, UK

\textsuperscript{f} Supplemental data for this article can be accessed here.

\textcopyright{} 2020 British Society of Audiology, International Society of Audiology, and Nordic Audiological Society
It is unknown if coronavirus can cause hearing loss but there have been unsubstantiated and anecdotal cases reported in national newspapers (Knibbs 2020). Therefore, this rapid systematic review investigated the presence and incidence of audio-vestibular symptoms as a result of coronavirus. A “rapid systematic review” is an accepted means of producing information in a timely manner (in this case over a period of three weeks) prior to submission so that timely evidence for decision-making purposes can be made available on this urgent and emergent health issue.

**Method and analysis**

The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020184932). The review method was described according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA-P) guidelines (Shamseer et al. 2015).

**Eligibility criteria**

The population of interest was patients who were diagnosed with coronavirus (i.e. SARS-CoV-2, Middle East respiratory syndrome [MERS] or severe acute respiratory syndrome [SARS]) using any diagnostic tool for coronavirus. Patients diagnosed with non-coronavirus infections were excluded. Patients should also be diagnosed with any audio-vestibular disorders as a result of coronavirus. The primary outcome of interest was any measurable change in hearing status. Secondary outcomes of interest were any reported tinnitus, hyperacusis or vertigo complaints. Prospective and retrospective randomised and non-randomised controlled trials were included. Cohort, cross-sectional, case report and case-control studies were also included.

**Information sources**

A systematic literature search of PubMed and the databases available in the Cochrane Library were used to identify relevant studies. Grey literature searching was undertaken in ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP WHO) search portal, targeted sites from Canadian Agency for Drugs and Technologies in Health (CADTH) Grey Matters and the preprint server for health sciences (Medrxiv). Google Scholar was used to identify further grey literature. Reference lists and citation tracking were screened to identify any additional relevant studies.

**Search strategy**

The search strategies were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The strategies utilised a combination of controlled vocabulary (e.g. “Coronavirus Infections”, “Hearing Loss”, “Deafness”) and free text (e.g. “Covid-19”, “SARS”, “SSHL”). Vocabulary and syntax were adjusted across selected databases. There was no date or language restrictions on any of the searches but when possible, animal-only records were removed from the results and interfaces. The full search strategy is reported in Supplementary material 1.

**Data management and selection process**

The retrieved references were exported to an Excel (2016) spreadsheet. After all duplications were removed the records were screened for the eligible criteria. The full text was inspected in all studies that met the inclusion criteria by two of the authors. Any disagreements were resolved by discussion. The screening process and results were summarised in a PRISMA-P flow diagram.

**Data collection process and data items**

The data were extracted by one specific author and verified by one other author, and discrepancies were resolved by discussion. Using a pre-design data extraction sheet, the following data were extracted from all the eligible studies: author(s), publication year, setting, peer-reviewed (or not), design (e.g. randomised controlled trial), participant demographics, outcomes and other important data. A web extraction tool (i.e. WebPlotDigitizer) was used to extract the data from the graphical format data.

**Risk of bias individual studies**

The risk of bias was assessed independently by two of the review team using the National Institutes of Health’s (NIH) quality assessment tools, which were designed to assess the risk of bias in epidemiological observational studies (the expected design of almost all the identified studies) and many other types of study (NIH National Heart, Lung and Blood Institute 2014). These tools provide a different checklist for each study design (e.g. Quality Assessment Tool for Case Series Studies and Controlled Intervention Studies). The quality of each study was rated as either good, fair, poor. The overall rating of each reviewer was reported.

**Data synthesis**

The identified studies were limited in number, so we narratively synthesised the data instead of quantitatively synthesising in a meta-analysis.

**Results**

**Search and selection of studies**

We initially identified more than 3,700 records, of which 1,420 were duplicates. The titles and abstracts (if available) of the remaining 2,371 records were screened against the inclusion criteria. Of these, 36 met the eligibility criteria. The full texts of those records were then inspected, and only six articles were deemed eligible for inclusion. One additional study was identified through other resources (i.e., other related COVID-19 reviews). The screening process and results are depicted in a PRISMA-P flow diagram (Figure 1).

**Characteristics of the included studies**

The characteristics and main audio-vestibular findings of the seven studies are shown in Table 1. All studies were published in 2020, and all of them are related to the novel coronavirus, SARS-CoV-2. Three were based in China (Cui et al. 2020; Han et al. 2020; Sun, Liu, and Wang 2020), one in Egypt (Mustafa
2020), one in Thailand (Sriwijitalai and Wiwanitkit 2020), one in Turkey (Fidan 2020), and one multisite study in Europe (France, Italy, Spain, Belgium, and Switzerland; Lechien et al. 2020). Of these, five were case reports (Cui et al. 2020; Fidan 2020; Han et al. 2020; Sriwijitalai and Wiwanitkit 2020; Sun, Liu, and Wang 2020) and two were cross-sectional studies (Lechien et al. 2020; Mustafa 2020). All but one study (Sriwijitalai and Wiwanitkit 2020) reported the age of the identified cases and almost all of them were adults. Although medications could cause audiovestibular symptoms, these were not reported in Table 1 because the details were frequently missing from the studies.

Diagnosis of coronavirus

Three studies used both reverse transcription-polymerase chain reaction (RT-PCR) and computed tomography (CT) to diagnose coronavirus (Fidan 2020; Han et al. 2020; Sun, Liu, and Wang 2020). Two studies used only RT-PCR (Lechien et al. 2020; Mustafa 2020), and the remaining two did not report the method for diagnosis (Cui et al. 2020; Sriwijitalai and Wiwanitkit 2020).

Audio-vestibular symptoms

Hearing loss was reported in four studies (N = 23 patients; Fidan 2020; Mustafa 2020; Sriwijitalai and Wiwanitkit 2020; Sun, Liu, and Wang 2020). The types and severity of hearing loss experienced by those infected with SARS-CoV-2 were reported in three studies. One reported a patient with binaural sensorineural hearing loss (with no additional details) but it is unclear if this was a pre-existing symptom (Sun, Liu, and Wang 2020), and the other reported a patient with unilateral mild-to-moderate conductive hearing loss due to acute otitis media (Fidan 2020). The remaining study compared two groups of patients (asymptomatic SARS-CoV-2 vs. control), and the author found that the asymptomatic SARS-CoV-2 group had significantly poorer hearing thresholds at 4–8 kHz and lower amplitude transient evoked otoacoustic emissions (t-OAE’s; Mustafa 2020).

Tinnitus was reported in four studies (N = 8 patients; Cui et al. 2020; Fidan 2020; Lechien et al. 2020; Sun, Liu, and Wang 2020). The characteristics of the tinnitus and the impact on the individual were not reported.

Rotatory vertigo was reported in two studies (N = 7 patients; Han et al. 2020; Lechien et al. 2020). It was not uncommon for
Table 1 summarises the overall quality rating for each of the included studies. In the three-category scale of quality (good, fair and poor), four were reported as fair and three as poor. There was a complete agreement between the two independent assessors. The full assessment checklists are reported in Supplementary material 3.

### Discussion

The aim of this rapid systematic review was to identify if COVID-19 affects the audio-vestibular system. A limited number of studies reported audio-vestibular symptoms, and the details were poorly described. The incidence of the reported audio-vestibular symptoms was below 1%, indicating that either these symptoms are uncommon or attention, so far, has concentrated on life-threatening symptoms. The incidence of audio-vestibular symptoms between those infected with other types of coronavirus (i.e. MERS and SARS) is unknown. Indeed, no records of audio-vestibular symptoms were identified in the literature with either MERS or SARS. This can be partially explained by the low incidence of these two types of coronaviruses relative to SARS-CoV-2.

The dearth of specific details on audio-vestibular symptoms is a common feature of the studies reported here. For example, Sun, Liu, and Wang (2020) reported a single case presenting with bilateral hearing loss and tinnitus without further details and it is unclear if this was a pre-existing symptom. Similarly, Mustafa (2020) and Siwjitjalai and Wiwanitkitb (2020) did not report the type or severity of the hearing loss (although it has been speculated that a possible cause is a thrombosis in the inner ear; Cure and Cure 2020). In addition, major flaws in the design (e.g. adults with gold standard hearing were used as a control group) of one of the cross-sectional studies were also observed (Mustafa 2020). Underreporting of important details about audio-vestibular symptoms, along with the other identified limitations, reduces our ability to interpret and synthesise these results.

Treatments used for COVID-19 might cause damage to the audio-vestibular system. For instance, hydroxychloroquine and chloroquine were prescribed for almost 12% of COVID-19 patients in Europe (Lechien et al. 2020). These antiviral medications have known adverse events, including tinnitus and hearing loss (Bortoli and Santiago 2007; FDA 2017; Prayuenyong, Kasbekar, and Baguley 2020) and the symptoms may be misdiagnosed as being caused by COVID-19.

Although the full text for all studies that reported an association between COVID-19 and Guillain Barre Syndrome (GBS) was screened, none of them mentioned symptoms consistent with ANSD. This is not unexpected because identification of studies to report dizziness as a clinical feature of COVID-19; however, the studies were not sufficiently specific for the symptoms to be considered vestibular in origin. The reference list of these studies is reported in Supplementary material 2.

Other ear-related symptoms, such as otalgia (ear pain), were reported in two studies (N = 359 patients; Fidan 2020; Lechien et al. 2020). Otitis externa was reported in one study (N = 1 patient; Cui et al. 2020), and otitis media was documented in another (N = 1 patient; Fidan 2020). Hyperacusis was not reported in any of the studies.

### Quality appraisal

The characteristics and main findings of the included studies.

<table>
<thead>
<tr>
<th>Authors, publication year, country</th>
<th>Participants</th>
<th>Study design</th>
<th>Audio-vestibular symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui et al. (2020), China</td>
<td>N = 20 (11M; 9F) Confirmed Covid-19 cases</td>
<td>Case report</td>
<td>Tinnitus (N = 1; 5%)</td>
</tr>
<tr>
<td>Fidan (2020), Turkey</td>
<td>N = 1 (F) Confirmed Covid-19 case</td>
<td>Case report</td>
<td>Otitis externa (N = 1; 2%)</td>
</tr>
<tr>
<td>Han et al. (2020), China</td>
<td>N = 1 (M) Confirmed Covid-19 case</td>
<td>Case report</td>
<td>Acute otitis media and conductive hearing loss</td>
</tr>
<tr>
<td>Lechien et al. (2020), Europe</td>
<td>N = 1420 (458M; 962F) Confirmed Covid-19 cases</td>
<td>Cross-sectional</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Mustafa (2020), Egypt</td>
<td>N = 20 (age range 20 to 50 years)</td>
<td>Case report</td>
<td>Sensorineural hearing loss (N = 1; 1.2%)</td>
</tr>
</tbody>
</table>

Table 1. The characteristics and main findings of the included studies.
ANSD requires a comprehensive audiological assessment, which may not be readily available during the lockdown period.

The quality of the studies in the review was rated as fair to poor due to underreporting (i.e. very short case reports) and major flaws in study methodology. This is a common observation in the current COVID-19 literature, where many articles appear to be published in an unusually rapid manner, perhaps lacking the rigour of peer-review.

Conclusion

Reports of audio-vestibular symptoms in confirmed COVID-19 cases are few and the publications are of poor quality. Emphasis over time is likely to shift from life-threatening concerns to longer term health-related consequences such as audio-vestibular dysfunction. High-quality studies are required in different age groups to investigate the acute effects of coronavirus, including temporary effects that may be caused by, for example, medication, as well as for understanding long-term risks, on the audio-vestibular system. We will update this systematic review in due course.

Acknowledgements

The authors thank Jun Xia for her constructive comments on the protocol of this review. We also thank Becky Skidmore, the information specialist, for developing the search strategy for this rapid systematic review. Sincere thanks to the three anonymous reviewers who provided very helpful comments in a very timely manner.

Disclosure statement

The authors declare no conflict of interest.

Funding

IA is partially funded, and KJM and KU are supported, by the NIHR Manchester Biomedical Research Centre [under Grant number IS-BRC-1215-20007]. IA is also supported by the Deanship of Scientific Research at the College of Applied Medical Sciences. IA is partially funded, and KJM and KU are supported, by the NIH National Heart, Lung and Blood Institute. The authors declare no conflict of interest.

ORCID

Ibrahim Almufarrij https://orcid.org/0000-0003-4043-7234
Kevin J. Munro https://orcid.org/0000-0001-6543-9098

References

NIH National Heart, Lung and Blood Institute. 2014. Study Quality and Clinical Considerations Systematic review. Sincere thanks to the three anonymous reviewers who provided very helpful comments in a very timely manner.