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CLINICAL NOTE

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Four cases of audio-vestibular disorders related to immunisation with SARS-CoV-2 mRNA vaccines

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ABSTRACT

Objective: To gain medical insight into the clinical course and safety of otolaryngologic disorders following immunisation with severe acute respiratory coronavirus (SARS-CoV-2) mRNA-based vaccines.
Design: Case description.
Study sample: We report four cases of transient audio-vestibular symptoms, which occurred shortly after inoculation of two BNT162b2 (Pfizer-BioNTech®) and mRNA-1273 (Moderna®) vaccines.
Results: Hearing loss was unilateral in all cases and recovered at least partially: it was associated with persistent gait instability in two cases, after 1 and 7 months. Trigger mechanisms underpinning audio-vestibular impairment remain uncertain. Immune tolerance mechanisms with off-target innate activation of T-lymphocytes may be involved in vestibulocochlear nerve disorders, as for other cranial nerves involvement.
Conclusions: The occurrence of audio-vestibular manifestations following mRNA-based vaccines needs ENT monitoring to support their causality in such rare vaccine-related adverse events. Audio-vestibular disorders appeared of transitory nature, including hearing loss, and should not deter further efforts in large-scale vaccination campaigns against SARS-CoV-2.

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Introduction

The worldwide spread of the severe acute respiratory coronavirus (SARS-CoV-2) led the development of new mRNA-based vaccines, the BNT162b2 (Pfizer-BioNTech®) and the mRNA-1273 (Moderna®) vaccines. The efficacy and safety data reported from Phase 2 or 3 trials were promising for both of these vaccines (Polack et al. 2020; Baden et al. 2021). However, a higher incidence of cases of acute peripheral facial paralysis (Bell's palsy) was observed between the mRNA vaccines and the placebo group, with four and eight cases (<0.1%) of Bell's palsy, *versus* no and three cases (<0.1%) in the placebo groups for each vaccines (Baden et al. 2021; Comirnaty 2021; El Sahly et al. 2021). Due to a close temporal relationship and past history of Bell's palsy following H1N1 immunisation (Mutsch et al. 2004), the manufacturers of both of these vaccines mention acute peripheral facial paralysis as a possible vaccine-related adverse event in their labelling information (Comirnaty 2021; Spikevax 2021).

Safety issues regarding mRNA-based vaccines are under scrutiny (Lopez Bernal et al. 2021). A recent case series of otologic manifestations after mRNA vaccines identified sensorineural hearing loss (SNHL) as the most frequent otolaryngologic symptom that led patients to seek medical advice (Wichova, Miller, and Derebery 2021). On the other hand, a preliminary analysis of the US Vaccine Adverse Events Reporting System (VAERS) in search of a potential signal for audio-vestibular deficits associated with mRNA vaccines did not support an increased incidence of such events (Formeister et al. 2021). To date, an association between the new-onset or worsening of otologic symptoms with the COVID-19 pandemic or mRNA vaccines remains unclear.

We report four cases of audio-vestibular symptoms that occurred shortly after mRNA SARS-CoV-2 immunisation. We also performed a review of the current literature and pharmacovigilance data. All cases originated from spontaneous reports of physicians and were mostly investigated in an ambulatory setting. They were examined in Regional Pharmacovigilance Centres in Switzerland from March 2021 to January 2022, and reported to the Swiss Agency for Therapeutic Products (Swissmedic). All patients gave written informed consent for the publication of their cases. Clinical data and evolution of cases were documented from each physician's office. Bilateral otoscopy was performed in all cases, and further investigations including

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pure tone audiogram (PTA) or video head impulse test (VHIT) were done depending on physician's practice. The type of material (e.g. transducers) used for PTA varied according to cases, no specific protocols were reported and equipment's calibration was performed yearly. PTA was reproduced using GraphPad Prism version 9.1.0 (GraphPad Software, La Jolla, CA).

Case reports

Case 1

A 74-year-old man with a medical history of hypercholesterolaemia received the first dose of the SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech®). A few hours later, he complained of a left-sided tinnitus with progressive hearing loss without any other symptoms and was evaluated the following day. His medical history was relevant for a transient episode of right-sided tinnitus in a stressful context 25 years earlier with no audio-vestibular disorder since. The only ongoing therapy was gemfibrozil; no allergies were documented. Rhinopharyngitis or flu-like symptoms were not reported. The otoscopy was normal on both sides, as well as the head and neck examination. A PTA showed a pattern of presbyacousis-like mixed hearing loss on the left side (Figure S1). Two days later, he reported spontaneous resolution and a repeat PTA confirmed a significant improvement of both components of the hearing loss. The other ear was not further investigated. One month later, he received the second vaccine dose, initially well tolerated. However, 8 d later, he presented the recurrence of a left-sided hearing loss. His physical examination remained normal. A third PTA confirmed the recurrence of a mixed hearing loss in low-to mid-frequencies. Brain magnetic resonance imaging (MRI) targeting the internal auditory meatus showed no pathological findings. He underwent a 2-d course of oral prednisolone after which he reported a subjective complete recovery and no recurrence afterwards. Considering the favourable course of the symptoms, no follow-up PTA was performed. A diagnosis of left mixed hearing loss was concluded. Interestingly, the third booster dose was well tolerated, without recurrence of hearing loss.

Case 2

A 61-year-old woman with a medical history of hypertension and atrial fibrillation received the first dose of the SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech®). Five days later, she experienced an abrupt onset of vertigo with gait instability, nausea, vomiting and moderate headache, for which she was investigated in a hospital setting. She had no allergies, candesartan 8 mg/d was ongoing. Her physical examination was remarkable for a spontaneous horizontal nystagmus with a fast phase beating to the right and a positive Halmagyi's test towards the left. A VHIT revealed a decreased vestibulo-ocular reflex (VOR) gain of the left lateral semicircular canal (0.1 *versus* 0.86) suggestive of left superior vestibular nerve neuritis. The superior and posterior canals were not investigated and other vestibular function tests were not performed. Brain MRI was normal. Symptomatic and antiviral treatments were empirically introduced. Ten days after vaccination, she also reported a left-sided hearing loss. Otoscopy was normal bilaterally. The PTA revealed a slight SNHL in the higher frequency range on the left ear and normal hearing thresholds on the right side (Figure S2). Prednisone was introduced for 5 d and vestibular physiotherapy initiated. A diagnosis of idiopathic cochleovestibular deficit was retained. Nine weeks after symptoms onset, a follow-up VHIT showed a partial recovery (left VOR gain at 0.32 versus normal on the right side). The PTA showed symmetrical normal hearing thresholds, except a left-sided asymmetry at 3 kHz (Figure S2). After 7 months of follow-up, she reported a partial recovery of gait instability. She declined the vaccine second dose so far.

Case 3

A 61-year-old healthy woman received the second dose of the SARS-CoV-2 mRNA vaccine (Moderna®). Approximately 12 h after vaccination, she reported diplacusis (altered perception of a same tone presented alternatively to both ears and perceived as different pitches) and right-sided hearing loss, along with flu-like symptoms (myalgia and malaise). Two days later, she sought medical advice due to the persistence of diplacusis and the development of mild episodes of rotatory vertigo associated with a single episode of vomiting. Her previous medical history was remarkable for a severe right vestibular neuritis 28 years earlier. No allergies or medications were reported. The oto-neurological examination was normal, in particular there was neither spontaneous nystagmus, nor focal neurological symptoms. A PTA revealed a right-sided moderate mixed hearing loss in low-to-mid frequencies (Figure S3). A short course of prednisone, quickly tapered, led to a rapid and complete recovery in a couple of days, confirmed on a follow-up PTA. Around 1 month post-vaccination, slight intermittent gait instability is described, but no recurrence of hearing loss. No recurrence of hearing loss was reported after a vaccine booster with the other SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech®) 8 months after the second dose.

Case 4

A 61-year-old healthy woman received the second dose of the SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech). Approximately 24 h later, she reported right-sided hearing loss with altered perception described as metallic sounds with continuous rustling, and ear fullness. She did not manifest any other symptoms. Her previous medical history was unremarkable with no previous ENT history and no known allergies or medications reported. On the fifth day, the oto-neurological examination was normal and a PTA revealed a right-sided mixed hearing loss in low to mid frequencies with normal hearing thresholds on the left side (Figure S4). A therapy with prednisone, betahistine and transtympanic steroid administration was initiated. A PTA performed 1 month later confirmed a partial recovery of the hearing loss and the ear fullness resolved. After 8 months of follow-up, only a partial subjective recovery was reported. She declined the vaccine third booster dose so far.

Discussion

Except for Bell's palsy, few case series report a possible causality between ENT symptoms and COVID-19 mRNA vaccines. First published cochlear disorders are three case reports of tinnitus occurring shortly following immunisation with the Pfizer/BioNTech vaccine. Symptoms occurred between 7 and 20 h after the first dose in two cases and seven days after the second dose in the latter one. One patient was known for SNHL in the past, while the others had no significant otolaryngologic medical history (Parrino et al. 2021). A recently published retrospective case series addressing otologic safety after mRNA-based vaccination

identified 30 cases of audio-vestibular manifestations. Hearing loss, the most frequent symptom, was reported in 25 (83%) patients, with a mean time-to-onset (TTO) of 10 d (range: 1–42 d). Eleven (37%) were known for previous otolaryngologic diagnosis. Three cases of positive rechallenge were observed in this case series, two in patients known for Menière's disease and one for an associated autoimmune inner ear disease, which could suggest underlying predisposing immunologic factors. Duration of symptoms was not detailed in this case series (Wichova, Miller, and Derebery 2021). Another case series described the occurrence of SNHL in three patients following immunizations with the Pfizer/BioNTech vaccine ($n = 2$) and adenoviral vector vaccine Oxford-AstraZeneca ($n = 1$) (Jeong and Choi 2021). The TTO ranged from 0 to 3 d post-immunisation, and occurred after the first dose in two cases and after the second dose in one case. One patient had an unfavourable course despite a dual therapy with systemic and local steroids. Of note, the authors suggest to prefer intratympanic steroids (ITS) instead of systemic steroids to avoid negative effects on antibodies titres (25). Additionally, some other publications have related the occurrence of otololaryngologic manifestations including SNHL with inactivated COVID-19 vaccines (Sinovac®, CoronaVac®, Vaxzevria®) similarly as to mRNA-based vaccines (Avcı et al. 2021; Tsetsos et al. 2021). For all these cases, the causal relationship remains unestablished.

Our cases indicate a close chronological relationship with immunisation, which suggests of a vaccine-related trigger phenomenon, similar to those reported in published series. Moreover, the positive rechallenge observed in case #1 strengthens the plausibility of causal relationship, scored *probable* according to the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al. 1981). Interestingly, the TTO observed in our cases was shorter than the mean TTO of 10 d previously reported (Wichova, Miller, and Derebery 2021). Symptoms occurred within hours (<12–24 h) after immunisation in case #1, #3 and #4, and after several days in case #2 and after the second dose in case #1, suggesting that different immunological phenomenon could be involved.

Hearing loss was transient in three of our four patients. Of note, two of them had a previous history of audio-vestibular symptoms, which may represent a predisposing condition. Moreover, the conductive component observed in the PTA in three of our cases might suggest other contributing causes, such as middle ear effusion or eustachian tube dysfunction, for which further objective investigations would have been needed (e.g. middle ear reflex and tympanometry).

Unilateral SNHL has been associated with a wide variety of identifiable causes, such as viral agents (e.g. HSV-1), vascular, toxic, neoplastic, traumatic or autoimmune diseases, and with immunizations with non-mRNA vaccines in rare cases. However, the aetiology retained for most cases is often idiopathic (Carol Liu et al. 2020). Several cases of SNHL following classical vaccines have been reported (Huang et al. 2010). A unique large-scale pharmacoepidemiological study assessed the risk of SNHL following active immunisation with 28 different vaccines, but failed to detect any association that could support a causal link (Baxter et al. 2016). Reports of vestibular neuritis following immunisation are even more rare (Greco et al. 2014). Of note, the occurrence of facial paralysis inferred from trials was greater with mRNA-based vaccines compared to virus vector vaccine technologies (Cirillo and Doan 2021; Ozonoff, Nanishi, Levy 2021).

An analysis of data gathered up to February 2021 in VigiBase Database (the WHO global database of individual case safety reports (ICSRs)) first raised concerns for a potential safety signal associated with mRNA-based vaccines due to a disproportionate number of reported cases of hearing loss and tinnitus (Rausch, 2021). At that time, while more than 39 million people were considered fully vaccinated (Our World in Data 2021), a total of 164 cases of hearing loss associated with COVID-19 vaccines were reported. In this analysis, the median TTO was 1-d post-vaccination with a range from several minutes to 19 d post-vaccination. Most reports concerned mRNA vaccines with, respectively, 142 reports following the Pfizer/BioNTech, 15 cases following the Moderna and seven cases after the adenovirus-vector vaccines. Some reports referred terms such as dizziness, nausea, facial paralysis or feeling of numbness suggesting the involvement of other cranial nerves, such as the facial or vestibular nerve. Among these cases, four cases of positive rechallenge were also observed, as in our case #1. A query in the same database in August 2021 retrieved 5381 non duplicated ICSRs of 'hearing loss' after vaccination with a mRNA vaccine (for 1.9 billion persons fully vaccinated) (Uppsala Monitoring Center 2021). Out of these, information was complete for 4753 cases, where the median TTO was 2 d (interquartile range of 0–9 d). The suspected agent was the Pfizer/BioNTech vaccine in most cases (3466, 73%). Symptoms were reported as recovered or recovering in 22% of the ICRS, not recovered in 13%, recovered with sequelae in 1% and unknown in 64%. Data gathered within VigiBase come from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. Of note, it does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organisation.

Along with published case series, these cases provide different results compared to the preliminary pharmacoepidemiological analysis that found no association between mRNA vaccine immunisation and increased risk of SNHL (Formeister et al. 2021). Epidemiological studies are subject to underreporting bias, which introduce limitations for conclusive assessment of causality, especially for rare adverse events (Layton, Key, and Shakir 2003).

Even though pathophysiological mechanism for otologic disorders related to mRNA-based vaccines are lacking, several hypotheses are raised. First, cochleovestibular symptoms after COVID-19 infection were observed in a systematic review and suggest a SARS-CoV-2 neurotropism for the cochleovestibular nerve (Almufarrij and Munro 2021). Second, autoimmune processes involving autoreactive T-lymphocytes and a transient break of peripheral immune tolerance mediated through vaccine antigen molecular mimicry could enhance isolated inflammation of the vestibulocochlear or facial nerve (Ozonoff, Nanishi, Levy 2021; Rausch 2021). The rapid onset of hearing loss observed strengthen this hypothesis. Further assumptions include reactivation of latent viruses following immunisation, as also postulated for vestibular neuritis (Greco et al. 2014; Wichova, Miller, and Derebery 2021), whereas endothelial disorders with a focal damage to cochlea capillaries or an immunisation anxiety-related reaction have also been postulated as possible causes of tinnitus associated with mRNA-based vaccines (Parrino et al. 2021). Finally, an IgG mediated immune off-target reaction directed against the vestibulocochlear nerve could be a possible mechanism where a mean TTO of 10 d was observed (Wichova, Miller, and Derebery 2021). However, the latter hypothesis fails to explain cases where symptoms occur shortly (sometimes within minutes) after the immunisation, notably for patients receiving the first dose and without previous COVID-19 infection. Interestingly, mixed hearing loss has not been reported after vaccination to our knowledge. SARS-CoV-2 tropism for middle ear mucosa, vestibular hair and Schwann cells (Frazier et al., 2020;

Jeong et al. 2021) suggests that transient middle ear effusion could also occur, in addition to inner ear inflammation. Middle ear effusion or infection signs were not reported in these four cases, and further investigations were not performed to confirm the absence of middle ear effusion.

Fear of adverse reactions after immunisation is a potential limitation to achieve herd immunity (Schwarzinger et al. 2021; Yigit, Ozkaya-Parlakay, and Senel 2021) and limits spontaneous reports during post-marketing surveillance, which are essential to detect rare adverse events associated with mRNA vaccines. The large-scale vaccination campaign with many mRNA-based vaccines may further unveil very rare adverse events linked to immunisation, such as SNHL, which is as of today not mentioned in the product labelling for mRNA COVID-19 vaccines as a possible adverse event of mRNA vaccines (Comirnaty, 2021; Spikevax 2021).

In cases of idiopathic SNHL, the initiation of systemic steroids should not be precluded by a recent immunisation or ITS may be considered, according to current recommendations. The impact of systemic steroids on COVID-19 vaccines efficacy remains to be clarified (Briggs, Brenner, and Chandrasekhar 2021; Chang et al. 2021).

Conclusion

Unilateral audio-vestibular disorders occur after SARS-CoV-2 mRNA vaccination and appear reversible. Further epidemiological studies are needed to better define the incidence and autoimmunological mechanisms. These studies should include diagnostic audiology testing obtained by experienced audiologists in hospital settings using well-accepted clinical protocols. The benefits of the COVID-19 vaccination appear to outweigh the risks of audio-vestibular disorders, since reported cases are mostly transient with favourable outcome.

Informed consent

All four patients signed a written informed consent for the publication of clinical cases.

Disclosure statement

None to declare. PE, KD, LR, AC, FB, FG contributed to data collection and literature review. PE, KD wrote the manuscript, PE, KD, LR, PG interpreted data. LR, PG, SM, AC, FB, FG critically reviewed the manuscript.

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