Audiovestibular Disorders after COVID-19 Vaccine

Subjects: Otorhinolaryngology

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The SARS-CoV-2 vaccination campaign is probably one of the most historic public hygiene measures in modern medicine. The drama of the pandemic has forced the scientific community to accelerate the development and commercialization of vaccines, thereby enhancing the phases of active surveillance. Among the adverse events following immunization (AEFI) reported, those of an audiovestibular interest, such as sudden sensorineural hearing loss (SSNHL), tinnitus, dizziness, and vertigo, constitute a very small percentage.

Keywords: COVID-19 ; vaccine ; adverse event ; SSNHL

1. Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was a massive global health concern which had a devastating impact on public health, economy, and social life worldwide. The COVID-19 phenotype is highly heterogeneous: it ranges from asymptomatic to severe and/or with fatal manifestations. The effectiveness of the immune system is the key to overcoming the disease. Unfortunately, hyperactivated immune responses, which can lead to respiratory insufficiency and other complications such as thrombotic or thromboembolic events, are not uncommon, given the possibility of SARS-CoV-2 to activate both the innate and acquired immune response [1].

The first months of the pandemic forced drastic containment measures, such as lockdowns due to the limited effectiveness of the proposed therapies [2][3]. Consequently, the entire scientific community focused on the development of vaccines capable of preventing severe forms of the disease.

Since December 2020, less than a year from the first reported case of COVID-19, several vaccines against SARS-CoV-2 have been authorized for emergency use [4].

In total, four types of COVID-19 vaccines were released: whole virus (live attenuated, inactivated), nucleic acid (mRNA, DNA), viral vector (non-replicating, replicating), and protein-based (subunit, virus-like particle) vaccines [5].

Whole virus vaccines are based on a weakened or inactivated phenotype of SARS-CoV-2 to trigger immunity; the nucleic acid vaccines introduce mRNA or DNA into the cells in order to induce production of antibodies against the SARS-CoV-2 spike protein; viral vector vaccines use a chemically weakened virus (e.g. adenovirus) to insert the code for SARS-CoV-2 antigens into the cells; and protein subunit vaccines are based on the spike protein or its antigenic fragments [6].

Vaccines undergo a long process of validation to ensure their efficacy and safety before being administered to a large-scale population. This process requires randomized, controlled, double-blind clinical trials, as well as a precise comparison of incidence of adverse events between the study-group and the placebo-group, all of which takes a long time, in order to demonstrate the effectiveness and safety [7].

The worsening of global development during the COVID-19 pandemic placed pressure on shortening this process to introduce possible life-saving vaccines; starting from December 2020, the first emergency approval was granted in the United Kingdom and the United States, shortly followed by Europe [8][9][10].

2. Discussion of Audiovestibular Disorders after COVID-19 Vaccine

The adverse effects of vaccines are mostly mild and self-limiting; pain at the injection site, redness or swelling at the injection site, fever, lymph node inflammation, headache, myalgias, joint pain, fatigue, and chills are the most common reported events. [11].

Most of the current vaccines against SARS-CoV-2 make use of the genetic code of the virus' spike protein to stimulate a protective immune reaction. The adenovirus used in viral vector vaccines (Vaxzevria, Oxford-AstraZeneca, UK; Sputnik, Gamaleya Research Institute of Epidemiology and Microbiology, Russian Federation; Janssen, Johnson & Johnson, USA) incorporates the spike protein gene into its DNA, inducing S-protein formation, which leads to antibody production; this process confers protection against the virus. Conversely, mRNA vaccines (Comirnaty, Pfizer-BioNTech, USA-Germany; Spikevax, Moderna) allow the mRNA for spike protein to enter the host cells, stimulating an intense immune response. Other COVID-19 vaccines (BBIBP-CorV, Sinopharm, China; CoronaVac, Sinovac Biotech, China) use weakened or attenuated forms of the virus, which can still replicate, but not sufficiently to cause the disease itself in immunocompetent hosts [12].

The mRNA vaccine can elicit a self-adjuvating mechanism, causing the mRNA to act as both antigen and adjuvant at the same time. This could trigger an autoimmune reaction resulting in type I interferon production, which leads to a strong T- and B-cell response and an autoreactive lymphocytes activation [13].

A cross-reactivity, due to the phenomenon of molecular mimicry, between anti-spike SARS-CoV-2 antibodies and ear antigens is a possibility that could link COVID-19 vaccines to audiovestibular AEFI [14][15].

Audiovestibular COVID-19 AEFI are quite uncommon, but the literature shows growing evidence that SSNHL, tinnitus, and vertigo can be observed after immunization.

Despite this, only a few articles passed the inclusion criteria. This highlights poor attention to the timely collection of clinical data, together with objective instrumental evaluations.

Among the selected papers, seven were related to SSNHL following COVID-19 immunization, mainly with associated tinnitus [16][17][18][19][20][21][22].

Several reports of SSNHL after immunization with commonly used vaccines, such as rabies, hepatitis B, measles, and H1N1, are currently reported in the literature [23][24][25][26][27][28].

The estimated incidence of SSNHL is between 5 and 30 cases per 100,000 [29]. Interestingly, Wichova et al. [16] found an SSNHL incidence of 3.85% among patients evaluated during their clinical practice in 2021. These researchers shared their retrospective data, affirming that SSNHL increased from 2019 to 2021, proposing the possibility of an association between COVID-19 or COVID-19 vaccination and SSNHL. However, the causality of this relationship remains unverified. The researchers failed to specify the grade of SSNHL, as well as the response to treatment. Moreover, they found an interesting concordance between the onset of symptoms and the development of post-vaccine immunoglobulin G (IgG). The time frame may coincide with the onset of IgG production, which usually appears 10 to 14 days after priming [30].

This led the researchers to hypothesize a possible autoimmune aetiology, according to the mechanism of cross-reaction. This hypothesis has been further corroborated by the collection of clinical data on patients with autoimmune diseases diagnosed before the vaccine which worsened following the vaccine. Moreover, the mean time of symptom onset did not change when comparing with a sub-group of patients with previous autoimmune inner ear disease (AIED) and Meniere's disease (MD) diagnoses.

A limitation of this thesis is the absence of RT-PCR testing which could rule out COVID-19 infection in these patients. In fact, if not clearly excluded from a negative nasopharyngeal swab, there is a reasonable suspicion that symptoms are due to a new SARS-CoV-2 infection, which is known to be characterized by high neural tropism with potential damage to the inner ear, even in mild forms [31][32][33].

Similar to the viral effect on neural pathways of the olfactory sense [34], vertigo or hearing loss are known sequelae of viruses. Goddard et al., for example, found herpes simplex virus (HSV) DNA in the vestibular nerve fibres of patient suffering from VN [35].

The spectrum of neurologic syndromes caused by COVID-19 includes encephalitis, demyelination, and Guillain-Barré syndrome [36]. These pathologies could have a rationale even as AEFI, likely related to processes of vaccine vector particle dissemination in the tissues and through the blood circulation, as well as through the alteration of the blood–brain barrier in case of intense inflammatory reactions [37].

Tsetsos et al. hypothesized a thrombotic aetiology (or vasospasm) of the SSNHL case they reported, which was an adult female with multiple cardiovascular risk factors [17].

Dysregulation of the cochlear blood flow due to altered plasma viscosity, cellular and platelet aggregability, red blood cell deformability, and endothelial function have all been observed in patients affected by SSNHL [38].

Therefore, it is likely that these events will occur in the older population who get vaccinated, representing the result of a physio-pathological phenomenon that naturally takes place, rather than being direct consequence of vaccine administration [39].

Chen et al. postulated that the viral antigen–antibody complex triggers a hypersensitivity reaction, which can lead to a localised inflammation that damages the inner ear microvessels [40].

The SARS-CoV-2 spike protein is an effective activator of the complement alternative pathway, which may contribute to endothelial damage, and is an enhancer of platelet aggregation, leading to thrombus formation [41].

Sessa et al. analysed the reports of thromboembolic events following vaccination with the Pfizer-BioNTech or Moderna COVID-19 vaccines, compared to hormonal contraceptive use (known to be associated with an increased but accepted risk of thromboembolic events), and found a much higher safety profile in vaccines [42].

Another useful consideration is the good response to treatment; the responsibility of micro-thromboembolism due to COVID-19 vaccines would be less likely, since steroids do not have any anti-thromboembolism effects.

Among the possible causes favouring SSNHL, it is also necessary to mention those of a genetic nature, both in syndromic and non-syndromic forms [30][43]. They could be linked to increased susceptibility to ototoxic drugs known to be used during the pandemic [44][45].

The aetiopathogenesis of tinnitus is still debated. Here, researchers noted that well-documented cases of tinnitus without hearing loss are rare. This seems to comply with a cortical reorganization due to sensorial deprivation as the most probable cause of tinnitus [46].

The cause of a possible increase in tinnitus during the pandemic may be increased anxiety and stress, since they share the same brain functional areas assigned to adaptive responses to sound stimuli [47]. Anzivino et al. postulated that an immunization anxiety-related reaction can be expected: anxiety has also been related to the severity and persistency of tinnitus, and it was found to be reasonable that the absence of environmental masking sound from everyday life should increase tinnitus perception [48].

Ueda et al. found a 45% reduction in the total number of vertigo-associated outpatient visits when comparing the period March–May 2020 with the same period of the 2019 [49].

Lovato et al. found a higher incidence of MD diagnosed for the first time, during the COVID-19 pandemic; moreover, known MD patients increased the number of vertigo attacks and reported higher dizziness handicap inventory (DHI) values, as compared to the previous year. These findings could be easily associated with the stress and higher anxiety present during the pandemic but could also relate to factors that could activate or boost the pathogenic mechanism of MD [50].

Vertigo and dizziness are two phenomena which are difficult to analyse in this research, since they are symptoms that are often reported without audiovestibular pathologies.

Few studies have been carried out with sufficient scientific accuracy, including Di Mauro et al., which had extreme difficulty in trying to homogenize a heterogeneous and small sample [51].

One important limitation researchers found in almost all screened papers was the lack of reporting of previous SARS-CoV-2 infection in the patients under study, or an incomplete pharmacological history. Moreover, only 2 studies out of 11 included RT-PCR testing to rule out possible SARS-CoV-2 infection.

These uncertainties that emerge from the literature could generate vaccine hesitancy and reluctance in the population. Surprisingly, in some cases, a certain hesitation or mistrust towards the vaccination campaign has been expressed even by health care workers, revealing an irrational fear, even in a professional category notoriously accustomed to experimental verification, towards the calculation of the cost/benefit, characterized by high resilience, especially during the pandemic [52][53].

Lastly, researchers suggest considering the emotional aspects of the pandemic and immunization campaign. As most of the reports in the major reporting systems are anecdotal, some of them are surely related to psychological and emotional aspects. The WHO defined the “anxiety-related adverse events following vaccination” as a “range of symptoms and signs that may arise around immunization that are related to anxiety and not to the vaccine product, a defect in the quality of the vaccine or an error of the immunization program” [54]. The Immunization Division of the Indian Ministry of Health and Family Welfare calculates that anxiety-related events account for up to 25% of total reports, including vasovagal-mediated reactions, hyperventilation mediated reactions, and stress-related psychiatric reactions or disorders [55].

This finding correlates with Zhang et al., who found that the most common AEFIs reported in a double-blind placebo-controlled clinical trial were pain, fever, and fatigue in the first 14 days after injection, both in the vaccination and placebo groups [56].

To date, none of the evaluated papers have unequivocally demonstrated a causal link between the COVID-19 vaccine and audiovestibular AEFI.

What the research of the literature makes apparent is the poor systemization of the data, which makes it difficult to aggregate cases, weakening the statistical power of the proposed theses.

All suspected COVID-19 AEFIs should be addressed to a specialist for rigorous audiovestibular assessment, and every report should be verified to collect as much standardized data as possible to increase the knowledge and increase the performance of systematic vaccine safety studies.

A proper identification, case study, and complete report is mandatory for enhancing the ongoing safety monitoring and supporting advances in mechanistic understanding.

Overall, the AEFIs are clearly outweighed by vaccine’s beneficial effects in decreasing hospitalization, mortality, and morbidity related to SARS-CoV-2 infection [57].

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