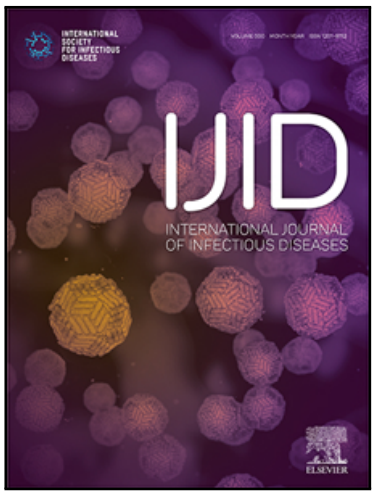

Facial nerve palsy following the administration of COVID-19 mRNA vaccines: analysis of self-reporting database

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Highlights

- A survey on facial nerve palsy following administration of COVID-19 mRNA vaccines.
- We statistically evaluated it using VAERS, a large self-reporting database.
- We observed significantly high reporting (reporting odds ratio: 1.84 and 1.54).
- Current results need to be validated in future observational studies.

Facial nerve palsy following the administration of COVID-19 mRNA vaccines: analysis of self-reporting database

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Running Title: Facial nerve palsy with COVID-19 mRNA vaccine

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Abstract

Objectives: Facial nerve palsy (or Bell's palsy) has rarely been reported following the administration of coronavirus disease 2019 (COVID-19) mRNA vaccines (BNT162b2 and mRNA-1273), which we investigated using large self-reporting data from the United States (Vaccine Adverse Event Reporting System [VAERS]).

Methods: For VAERS reports of individuals who were vaccinated at the age of 18 years or above between January 2010 and April 2021, we conducted a disproportionality analysis that was adjusted for age and sex.

Results: The analysis revealed that the adverse events following immunization (AEFI) of facial nerve palsy, after the administration of COVID-19 mRNA vaccines was significantly highly reported both in BNT162b2 (reporting odds ratio [ROR]: 1.84, 95% confidence interval [CI]: 1.65 ~ 2.06) and mRNA-1273 (ROR 1.54, 95% CI: 1.39 ~ 1.70). These were comparable levels to that following influenza vaccination reported before the COVID-19 pandemic (ROR 2.04, 95% CI: 1.76 ~ 2.36).

Conclusions: The current pharmacovigilance study results suggested that the incidence of facial nerve palsy as their non-serious AEFI may be fewer than or equivalent to that of influenza vaccines, which might be informative in the mid of worldwide vaccination promotions but needs to be validated in future observational studies.

Keywords: COVID-19; mRNA vaccine; facial nerve palsy; Bell's palsy; pharmacovigilance; VAERS

Introduction

Newly developed coronavirus disease 2019 (COVID-19) mRNA vaccines (i.e., BNT162b2 [1] and mRNA-1273 [2]) have shown a marked effect in preventing SARS-CoV-2 infection [3, 4]. While they frequently cause non-serious adverse events (AEs), such as fatigue, headache, chills, fever, and pain, serious AEs, such as anaphylaxis, have been rarely reported [1, 2].

Moreover, unilateral facial nerve palsy (or Bell's palsy) has been observed as a rare neurological AE in earlier clinical studies [1, 2] or reported in earlier case reports [5-7]. It is also known in the case of influenza vaccines that there was slightly increased reporting of facial nerve palsy after the administration of influenza vaccines [7, 8]. Although the reduction in lymphocytes, which can occur in COVID-19 infection, may trigger herpesvirus reactivation leading to facial nerve palsy, it remains uncertain whether COVID-19 mRNA vaccines cause facial nerve palsy. Facial nerve palsy may possibly be an AE event following immunization (AEFI) of COVID-19 mRNA vaccines, as such by the following possibility, for example, the combined effect of lipids and mRNA, leading to interferon production and the successive impairment of peripheral tolerance [7]. Herein, we aimed to statistically validate this point by analyzing the Vaccines Adverse Event Reporting System (VAERS) database, which contains a very large number of self-reported cases of individuals who received vaccines across the United States.

Methods

This study was approved by the University of Tokyo Graduate School of Medicine Institutional Ethics Committee [ID: 11754-(1)]. Informed consent was not required for this study. The following procedures were performed using R software (version 3.6.3) and were generally in accordance with our previous report [9]. We downloaded VAERS data from the US Food and Drug Administration website (https://vaers.hhs.gov) on May 8, 2021. We included the reported individuals who were vaccinated between January 1, 2010, and April 30, 2021, who were 18 years of age or older at the time of vaccination, and whose AEFI developed within 0-180 days after vaccination.

We classified each report based on the following binomial factors: "with" or "without" exposure to the administration of vaccines of interest (namely, BNT162b2 from Pfizer and BioNTec [1], and mRNA-1273 from Moderna [2], and any influenza vaccines as a reference), and "with" or "without" the development of an AEFI category of interest (i.e., facial nerve palsy), which was defined based on union of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of "Bell's palsy," "Bell's phenomenon," "Facial paralysis," "Facial palsy," "Facial asymmetry," and "Viith nerve paralysis."

For each vaccine, we calculated the reporting odds ratio (ROR) of the defined AEFI category "facial nerve palsy" using a logistic regression model as follows [9]:

$$log(odds) = \beta_a + \beta_b \cdot age + \beta_c \cdot sex + \beta_d \cdot vaccine$$

where $vaccine$ denotes binomial status (= 0 if not used, and = 1 if used) of the vaccine of interest. Since we could not deny the possible influence of the COVID-19 pandemic on the reporting behavior of influenza vaccines [10], we only included cases reported before March 2020 when examining influenza vaccines. When the lower 95% confidence interval (CI) of ROR was higher than 1, the AEFI (facial nerve palsy) was considered to be significantly higher following the administration of the vaccine of interest, when compared to the rest of the vaccines.

Results

Our analysis included 303,589 reports that followed the use of any vaccine. Across the reviewed period, facial nerve palsy was reported by 405 reports after BNT162b2, 512 reports after mRNA-1273, and 462 reports after any influenza vaccines. Before the emergence of COVID-19 mRNA vaccines, facial nerve palsy was mostly reported following influenza vaccine administration, while its rate greatly decreased by 2020 (Figure 1).

The adjusted ROR is summarized in Table 1, which reveals mildly but significantly high reporting of facial nerve palsy following the administration of BNT162b2 (ROR 1.84, 95% CI: 1.65 ~ 2.06) and mRNA-1273 (ROR 1.54, 95% CI: 1.39 ~ 1.70). Influenza vaccines showed a slightly higher ROR of 2.04 (95% CI: 1.76 ~ 2.36), which is comparable with earlier study results [7, 8]. The reported period from vaccination to the onset of facial nerve palsy was similar for these vaccines (median 3-4 days, with interquartile range 1-14 days) (Table 1).

Discussion

These results showed a statistically significant association between the administration of mRNA COVID-19 vaccines and the reporting of facial nerve palsy after vaccination, in line with a few earlier reports on facial nerve palsy after vaccination [5-7]. Our results might be informative for neurologists and physicians in the mid of worldwide promotion activities of COVID-19 vaccines.

Our approach has some limitations, due to the nature of the self-reporting database [9]: over- or under-reporting of AEFIs, the absence of denominators by which we cannot discuss the incidence rate of AEFI, and the lack of concomitant medications or medical histories. Therefore, currently, our study results should not be directly interpreted as the causal evidene of vaccination to cause facial nerve palsy.

Despite these weaknesses, the major strength of our study is that it was based on a database that includes global real-world data from a very large number of patients, being suitable for providing an early hypothesis to guide future epidemiological studies. In order to conclude whether COVID-19 mRNA vaccines truly increase the incidence of facial nerve palsy, further observational studies are required. In addition, it is uncertain how the facial nerve palsy after vaccination may differ from Guillain-Barré Syndrome (GBS) after COVID-19 infection in their underlying mechanisms, which also need investigation in the future.

The increase in the reporting of facial nerve palsy was mostly equivalent level as of that following the influenza vaccines reported before the COVID-19 pandemic; although underlying

mechanisms may differ, observing facial nerve palsy in this level of frequency might be informative for neurologists and physicians in the mid of worldwide promotion activities of COVID-19 vaccines.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

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The authors have no potential conflict of interest to disclose, specifically with regard to pharmaceutical companies that developed BNT162b2 (Pfizer and BioNTec) or mRNA-1273 (Moderna).

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Table

Table 1. Result summary of the facial nerve palsy reports.

Vaccine	N with facial nerve palsy and the use of vaccination across the period †	Adjusted ROR (95% CI)	Age of vaccination (median, IQR)	Sex (frequency and % of female)	Days from vaccination to onset (median, IQR)
BNT162b2	n = 405	1.843 (1.647 ~ 2.057)*	51 (39 ~ 66)	251 / 403 (62.28 %)	3 (1 ~ 10)
mRNA-1273	n = 512	1.536 (1.385 ~ 1.7)*	57 (44 ~ 70)	321 / 512 (62.7 %)	3.5 (1 ~ 14)
all influenza vaccines	n = 462	2.04 (1.763 ~ 2.363)*	49.5 (37 ~ 59)	282 / 461 (61.17 %)	4 (1 ~ 13)

All three vaccines showed significantly high reporting (lower 95% CI > 1) of facial nerve palsy.

(†) Note that the period for AEFIs following COVID-19 vaccines is from January 2020 to April 2021, while the period for AEFIs following any other vaccines is from January 2020 to February 2020.

Abbreviations: AEFI, adverse events following immunization; ROR, reporting odds ratio; CI, confidence interval; IQR, interquartile range.

Figure legends

Figure 1. Proportion (%) of each vaccine among annual facial nerve palsy reports. The annual proportion of influenza vaccines among all annual facial nerve palsy cases declined from 2019 to 2020-2021 (until April 31), as if the influenza vaccines were replaced by COVID-19 mRNA vaccines.