Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 111 (2021) 310–312

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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

Kenichiro Sato [1,2,3], Tatsuo Mano [1], Yoshiki Niimi [3], Tatsushi Toda [1], Atsushi Iwata [4,*], Takeshi Iwatsubo [2,3]

[1] Department of Neurology, Graduate School of Medicine, University of Tokyo
[2] Department of Neuropathology, Graduate School of Medicine, University of Tokyo
[3] Unit for Early and Exploratory Clinical Development, University of Tokyo Hospital
[4] Department of Neurology, Tokyo Metropolitan Geriatric Medical Center Hospital

ARTICLE INFO

Article history:
Received 18 May 2021
Revised 21 July 2021
Accepted 30 August 2021

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

ABSTRACT

Objectives: Facial nerve palsy (or Bell's palsy) has occasionally been reported following the administration of coronavirus disease 2019 (COVID-19) mRNA vaccines (BNT162b2 and mRNA-1273). Our study investigated such cases using a large self-reporting database from the USA (Vaccine Adverse Event Reporting System [VAERS]).

Methods: A disproportionality analysis, adjusted for age and sex, was conducted for VAERS reports from individuals who were vaccinated at the age of 18 years or over, between January 2010 and April 2021.

Results: The analysis revealed that the adverse events following immunization (AEFI) of facial nerve palsy, after administration of COVID-19 mRNA vaccines, was significantly highly reported, both for 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 levels were comparable to that following influenza vaccination reported before the COVID-19 pandemic (ROR 2.04; 95% CI 1.76–2.36).

Conclusions: Our pharmacovigilance study results suggest that the incidence of facial nerve palsy as a non-serious AEFI may be lower than, or equivalent to, that for influenza vaccines. This information might be of value in the context of promoting worldwide vaccination, but needs to be validated in future observational studies.

Introduction

Newly developed coronavirus disease 2019 (COVID-19) mRNA vaccines (i.e. BNT162b2 (US Food and Drug Administration 2021) and mRNA-1273 (US Food and Drug Administration 2021)) have shown marked effects in preventing SARS-CoV-2 infection (Polack et al., 2020, Baden et al., 2021). 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 (US Food and Drug Administration 2021, US Food and Drug Administration 2021).

Unilateral facial nerve palsy (or Bell's palsy) has been observed as a rare neurological AE in earlier clinical studies (US Food and Drug Administration 2021, US Food and Drug Administration 2021), or reported in earlier case reports (Cirillo, 2021, Repajic et al., 2021, Ozonoff et al., 2021). In the case of influenza vaccines, there has been slightly increased reporting of facial nerve palsy after their administration (Ozonoff et al., 2021, Kamath et al., 2020). Although the reduction in lymphocytes that 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 as an AE following immunization (AEFI) of COVID-19 mRNA vaccines might be the result of the combined effect of lipids and mRNA, leading to interferon production and the subsequent impairment of peripheral tolerance (Ozonoff et al., 2021). Our study aimed to statistically validate this point by analyzing the Vaccines Adverse Event

☆ Running title: Facial nerve palsy with COVID-19 mRNA vaccine

* Correspondence to: Dr Atsushi Iwata, Department of Neurology, Tokyo Metropolitan Geriatric Medical Center Hospital, Sakaecho, Itabashi-ku, Tokyo, Japan
E-mail address: iwata-tky@umin.ac.jp (A. Iwata).

https://doi.org/10.1016/j.ijid.2021.08.071

Table 1
Result summary of the facial nerve palsy reports

Vaccine	Number with facial nerve palsy following use of vaccination over the study period[†]	Adjusted ROR (95% CI)	Age at vaccination (median, IQR)	Sex (frequency and % 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 of facial nerve palsy (lower 95% CI > 1).
Abbreviations: AEFI, adverse events following immunization; ROR, reporting odds ratio; CI, confidence interval; IQR, interquartile range
[†] The period for AEFIs following COVID-19 vaccination was from January 2020 to April 2021, while the period for AEFIs following any other vaccines was from January 2020 to February 2020.

Reporting System (VAERS) database, which contains a very large number of self-reported cases of individuals who have received vaccines across the USA.

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 (Sato et al., 2019). VAERS data were downloaded from the US Food and Drug Administration website (https://vaers.hhs.gov) on May 8, 2021. 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 AEFIs developed within 0–180 days of vaccination, were included.

Each report was classified based on the following binomial factors: "with" or "without" exposure to the administration of vaccines of interest (namely, BNT162b2 from Pfizer and BioNTec (US Food and Drug Administration 2021) and mRNA-1273 from Moderna (US Food and Drug Administration 2021), 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 by combining the 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, the reporting odds ratio (ROR) for the defined AEFI category "facial nerve palsy" was calculated using a logistic regression model, as follows (Sato et al., 2019):

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

where *vaccine* denotes the binomial status (= 0 if not used, and = 1 if used) of the vaccine of interest. Since the possible influence of the COVID-19 pandemic on the reporting behavior for influenza vaccines could not be discounted (Dörks et al., 2021), only cases reported before March 2020 were included when examining influenza vaccines. When the lower 95% confidence interval (CI) of the 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 with 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 405 times after BNT162b2, 512 after mRNA-1273, and 462 after any influenza vaccine. Before the emergence of COVID-19 mRNA vaccines, facial nerve palsy was mostly reported following influenza vaccine administration, although this rate had greatly decreased by 2020 (Figure 1).

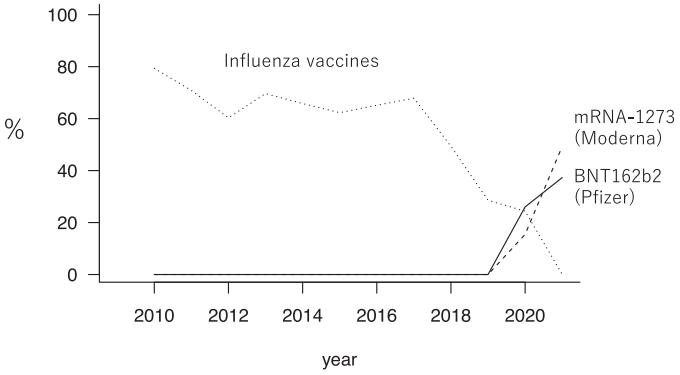

Figure 1. Annual proportion (%) of each vaccine type among facial nerve palsy reports. The annual proportion of influenza vaccines declined from 2019 to 2020/2021 (until April 31), with influenza vaccines appearing to be replaced by COVID-19 mRNA vaccines.

The adjusted RORs are summarized in Table 1; these revealed mild 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 was comparable with earlier study results (Ozonoff et al., 2021, Kamath et al., 2020). The reported period from vaccination to the onset of facial nerve palsy was similar for these vaccines (median 3–4 days; interquartile range 1–14 days) (Table 1).

Discussion

Our 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 some earlier reports on facial nerve palsy after vaccination (Cirillo, 2021, Repajic et al., 2021, Ozonoff et al., 2021). Our results might be informative for neurologists and physicians in the context of worldwide promotion of COVID-19 vaccines.

Our approach had some limitations, due to the nature of the self-reporting database (Sato et al., 2019). These included: over- or under-reporting of AEFIs; the absence of data on denominators that may have influenced the incidence rate of AEFI; and the lack of information on concomitant medications or medical histories. Currently, therefore, our study results should not be directly interpreted as evidence of vaccination causing facial nerve palsy.

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. Moreover, it is uncertain how facial nerve palsy after vaccination may differ from Guillain-Barré syndrome (GBS) after COVID-19 infection, in terms of their underlying mechanisms, which also need further investigation.

The level of reporting of facial nerve palsy after COVID-19 mRNA vaccination was generally equivalent to that following influenza vaccines prior to the COVID-19 pandemic. Although the underlying mechanisms may differ, observations of facial nerve palsy at this frequency might be informative for neurologists and physicians in the context of worldwide promotion of COVID-19 vaccines.

Funding

This study was supported by the Japan Agency for Medical Research and Development grants JP21dk0207057, JP21dk0207048, and JP20dk0207028, and by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 20J11009.

Conflicts of interest

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

Acknowledgments

This study was performed using the Vaccines Adverse Event Reporting System (VAERS) database provided by the US Food and Drug Administration (FDA). The presented information, results, or interpretation of the current study do not represent any opinions of the FDA.

References

US Food and Drug Administration. Fact Sheet for Healthcare Providers Administering Vaccine. EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19). https://www.fda.gov/media/144413/download, 2021 (accessed May 11, 2021)

US Food and Drug Administration. Fact Sheet for Healthcare Providers Administering Vaccine. EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19). https://www.fda.gov/media/144637/download, 2021 (accessed May 11, 2021)

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383(27):2603–15. doi:10.1056/NEJMoa2034577.

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403–16. doi:10.1056/NEJMoa2035389.

Cirillo N. Reported orofacial adverse effects of COVID-19 vaccines: the knowns and the unknowns. J Oral Pathol Med 2021;50(4):424–7. doi:10.1111/jop.13165.

Repajic M, Lai XL, Xu P, Liu A. Bell's palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell's palsy. Brain Behav Immun Health 2021;13. doi:10.1016/j.bbih.2021.100217.

Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. Lancet Infect Dis 2021;21(4):450–2. doi:10.1016/S1473-3099(21)00076-1.

Kamath A, Maity N, Nayak MA. Facial paralysis following influenza vaccination: a disproportionality analysis using the vaccine adverse event reporting system database. Clin Drug Investig 2020;40(9):883–9. doi:10.1007/s40261-020-00952-0.

Sato K, Mano T, Iwata A, Toda T. Neurological and related adverse events in immune checkpoint inhibitors: a pharmacovigilance study from the Japanese Adverse Drug Event Report database. J Neurooncol 2019;145(1):1–9. doi:10.1007/s11060-019-03273-1.

Dörks M, Jobski K, Hoffmann F, Douros A. Global COVID-19 pandemic and reporting behavior — an analysis of the Food and Drug Administration adverse events reporting system. Pharmacoepidemiol Drug Saf 2021;30(6):707–15. doi:10.1002/pds.5217.