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Association of COVID-19 Vaccination and Facial Nerve Palsy

A Case-Control Study

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Key Points

Question

Is the Pfizer-BioNTech BNT162b2 COVID-19 vaccine associated with increased risk of peripheral facial nerve palsy?

Findings

In this case-control study of 37 patients with acute-onset facial nerve palsy and a matched control group, no increased risk of facial nerve palsy was observed after vaccination. In addition, no meaningful increase in the number of admissions for facial nerve palsy was observed compared with preceding years.

Meaning

These outcomes suggest that recent vaccination with the BNT162b2 vaccine is not associated with an increased risk of facial nerve palsy.

Abstract

Importance

Peripheral facial nerve (Bell) palsy has been reported and widely suggested as a possible adverse effect of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine. Israel is currently the leading country in vaccination rates per capita, exclusively using the BNT162b2 vaccine, and all residents of Israel are obligatory members of a national digital health registry system. These factors enable early analysis of adverse events.

Objective

To examine whether the BNT162b2 vaccine is associated with an increased risk of acute-onset peripheral facial nerve palsy.

Design, Setting, and Participants

This case-control study was performed from January 1 to February 28, 2021, at the emergency department of a tertiary referral center in central Israel. Patients admitted for facial nerve palsy were matched by age, sex, and date of admission with control patients admitted for other reasons.

Exposures

Recent vaccination with the BNT162b2 vaccine.

Main Outcomes and Measures

Adjusted odds ratio for recent exposure to the BNT162b2 vaccine among patients with acute-onset peripheral facial nerve palsy. The proportion of patients with Bell palsy exposed to the BNT162b2 vaccine was compared between groups, and raw and adjusted odds ratios for exposure to the vaccine were calculated. A secondary comparison with the overall number of patients with facial nerve palsy in preceding years was performed.

Results

Thirty-seven patients were admitted for facial nerve palsy during the study period, 22 (59.5%) of whom were male, and their mean (SD) age was 50.9 (20.2) years. Among recently vaccinated patients (21 [56.7%]), the mean (SD) time from vaccination to occurrence of palsy was 9.3 (4.2 [range, 3-14]) days from the first dose and 14.0 (12.6 [range, 1-23]) days from the second dose. Among 74 matched controls (2:1 ratio) with identical age, sex, and admittance date, a similar proportion were vaccinated recently (44 [59.5%]). The adjusted odds ratio for exposure was 0.84 (95% CI, 0.37-1.90; *P* = .67). Furthermore, analysis of the number of admissions for facial nerve palsy during the same period in preceding years (2015-2020) revealed a relatively stable trend (mean [SD], 26.8 [5.8]; median, 27.5 [range, 17-35]).

Conclusions and Relevance

In this case-control analysis, no association was found between recent vaccination with the BNT162b2 vaccine and risk of facial nerve palsy.

This case-control study examines whether the Pfizer-BioNTech BNT162b2 vaccine is associated with an increased risk of acute-onset peripheral facial nerve palsy.

Introduction

COVID-19 is caused by SARS-CoV-2, and immunity can be achieved either by native or preventive immunization of the population. Thus far, the US Food and Drug Administration has issued an emergency use authorization for 3 novel COVID-19 vaccines.[1] On December 11, 2020, the BNT162b2 (Pfizer-BioNTech) vaccine was the first to achieve this authorization, and millions of people worldwide have been vaccinated with it.[2]

Peripheral facial nerve palsy has been reported and widely suggested as a possible adverse effect of the BNT162b2 vaccine.[3,4,5,6,7,8,9] This was initially prompted by the imbalance in peripheral facial nerve palsy cases reported in the original efficacy trial published in December 2019.[10,11] Peripheral facial nerve palsy was reported in 4 cases among the vaccinated participants and none of the controls.[10,11] Since then, several case reports and commentaries[4,5,6,7,8,9] and much media attention have been devoted to the subject,[3,5,6,12,13] yet robust evidence is scarce.

On December 19, 2020, Israel launched a national vaccination program. Israel is the leading country in vaccination rates per capita, with approximately 92% and 85% of the population older than 50 years immunized with the first and second doses, respectively, as of March 1, 2021.[14] At present, vaccination in Israel is promoted exclusively with the BNT162b2 vaccine. All residents of Israel are members of a national

digital health registry system. These factors provide a unique opportunity to perform an early real-world analysis of adverse events due to the BNT162b2 vaccine and report on an association or the lack thereof regarding peripheral facial nerve palsy after vaccination.

Methods

This study adhered to the tenets of the Declaration of Helsinki[15] and was approved by the institutional review board of the Shamir Medical Center. Owing to its retrospective nature, a waiver of informed consent was granted. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Design and Patient Population

The BNT162b2 vaccine was given emergency use authorization by the US Food and Drug Administration in early December 2020. It has been authorized for all individuals older than 16 years and is injected in 2 doses separated by a 21-day interval.

We conducted a case-control study examining the association between exposure to the BNT162b2 vaccine and facial nerve palsy. Cases were defined as patients who were admitted to the emergency department of a single tertiary referral center in Israel (Shamir Medical Center [formerly Assaf Harofeh], Tzrifin) and were diagnosed with new-onset peripheral facial nerve palsy from January 1 to February 28, 2021. In Israel, it is standard practice to refer all patients with new-onset peripheral nerve palsy for evaluation in the emergency department. Data were collected by a computerized hospital system according to *International Classification of Diseases, Ninth Revision*, code 351.0 (Bell palsy). We retrospectively reviewed each medical record and manually recorded rates and timing of vaccination with the BNT162b2 vaccine. Included were all patients who were older than 18 years and of any medical status. Controls were patients who had been admitted to the same emergency department for any reason other than facial nerve palsy and were matched for age, sex, and admission date within 48 hours.

Controls were matched for date of admission for 2 reasons. First, seasonality was found to be a risk factor for peripheral nerve palsy, and matching enabled us to exclude this as a possible bias between groups. Second, vaccines were being rolled out in Israel during this time, and later admission predisposed a given patient to a higher chance of being vaccinated. Matching for admission date was a way to ensure that timing was not a possible factor for bias.

Two controls were matched for each case and were randomly selected. In both groups, the percentage of patients exposed to the BNT162b2 vaccine (first or second dose) within the previous 30 days was calculated and the adjusted and unadjusted odds ratios (ORs) for exposure were compared with corresponding 95% CIs. Age, sex, and seasonality are risk factors for facial nerve palsy and are inherently controlled for

by the study design; however, existence of immune- or inflammatory-related disorders, diabetes, and a previous episode of peripheral nerve palsy are also implicated as possible risk factors. These factors were extracted, and an adjusted OR controlling for these factors was also calculated.

As a secondary analysis, all cases of facial nerve palsy during the same period (January to February) in the 6 preceding years were extracted according to *International Classification of Diseases, Ninth Revision*, codes and compared with 2021. The months of January and February were selected because the national vaccination campaign in Israel began on December 19, 2020, and by March 1, 2021, more than 92% of the population older than 50 years was already vaccinated with the first dose.[14] Thus, early postvaccination adverse events should be evident during this period. For this analysis, the data are presented as they are and the overall trend is presented without statistical analyses.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 25 (IBM Corp). Categorical variables such as sex and existence of diabetes were compared using the χ^2 test. Continuous variable distributions were tested for normality by the Shapiro-Wilk test. Independent 2-tailed *t* tests were conducted for continuous variables with a normal distribution and the Mann-Whitney test for continuous variables with a nonnormal distribution. The OR for exposure to the vaccine was calculated with the corresponding 95% CI. Two-sided $P < .05$ was considered statistically significant. For sample calculation, a case-control model was used with a CI of 0.95 and power was set at 80%. Assuming an exposed proportion of 0.6 among the controls and an expected OR of 4.00, the total sample size needed (in both groups) to detect a significant association was calculated to be 88 patients. Sample size calculations were performed using MedCalc software, version 17 (MedCalc Software Ltd).

Results

During the study period, a total of 37 patients were admitted for an acute-onset facial nerve palsy. The mean (SD) patient age was 50.9 (20.2) years; 22 (59.5%) were male and 15 (40.5%) were female. Most of the patients were discharged on the same day, and only 2 were admitted for further evaluation. Of the 37 patients, 4 (10.8%) had diabetes, 2 (5.4%) had immune- or inflammatory-associated disorders (familial Mediterranean fever and psoriasis), and 2 (5.4%) had a previous episode of peripheral facial nerve palsy. A detailed description of the cases is provided in Table 1. Comparing recently vaccinated (21 of 37 [56.7%]) with unvaccinated (16 of 37 [43.2%]) patients showed no meaningful difference in age (mean [SD], 55.5 [19.2] vs 44.9 [20.5] years; $P = .12$) or sex (13 [61.9%] male vs 9 [56.3%] male; $P = .73$). Among recently vaccinated patients who received only the first dose, the mean (SD) time from vaccination to occurrence of facial nerve palsy was 9.3 (4.2 [range, 3-14]) days; among those who completed the vaccination process with the second dose (10 of 37 [27.0%]), the mean (SD) time from vaccination was 14.0 (12.6 [range, 1-23]) days.

For each patient admitted with a case of new-onset peripheral facial nerve palsy, 2 matched controls were randomly selected. No meaningful differences were seen between the controls and cases in terms of a diagnosis of diabetes (4 of 37 [10.8%] among cases vs 15 of 74 [20.3%] among controls; difference, 9.5% [95% CI, −6.4% to 21.8%]), rates of immune- or inflammatory-related disorders (2 of 37 [5.4%] among cases vs 3 of 74 [4.1%] among controls; difference, 1.3% [95% CI, −6.8% to 13.9%]), and a previous episode of peripheral nerve palsy (2 of 37 [5.4%] among cases vs 0 of 74 among controls; difference, 5.4% [95% CI, −0.9% to 17.7%]). Overall, 21 of 37 individuals (56.8%) with facial nerve palsy were recently vaccinated with the first or second dose of the BNT162b2 vaccine, compared with 44 of 74 (59.5%) in the control group (Table 2). The unadjusted OR for exposure to the vaccine among cases was 0.90 (95% CI, 0.40-1.99; *P* = .79).

After adjusting for existence of immune- or inflammatory-related disorders, diabetes, and a previous episode of peripheral nerve palsy, the OR for exposure to the vaccine among cases was 0.84 (95% CI, 0.37-1.90; *P* = .67). In addition, we compared the overall number of patients with acute-onset facial nerve palsy with that of preceding years, before the advent of the COVID-19 pandemic or vaccine. Table 3 shows the number of cases of facial nerve palsy admitted during January and February of 2021 and in the same period during the 5 preceding years. A similar volume of admissions was seen in 2021 for facial nerve palsy compared with preceding years (mean [SD], 26.8 [5.8] cases; median, 27.5 [range, 17-35] cases).

Discussion

In this study, occurrence of acute-onset facial nerve palsy was evaluated for an association with recent SARS-CoV-2 vaccination with the BNT162b2 vaccine. In a case-control comparison with controls matched for age, sex, and date of admission, no association between facial nerve palsy and vaccination status was observed. In addition, when comparing the number of patients admitted for facial nerve palsy during the same period in preceding years, a similar volume of admissions is seen. These results are noteworthy given that the first vaccination occurred in Israel on December 19, 2020, and by March 1, 2021, more than 92% of the population of Israel older than 50 years was already vaccinated with the first dose.[14] Given even a small association of the vaccine with facial nerve palsy, a dramatic increase in cases should have been evident.

In the original BNT162b2 safety and efficacy trial published in December of 2020,[10,11] peripheral facial nerve palsy was reported in 4 cases among the vaccinated participants and none of the controls. Similar results were published later with regard to the messenger RNA (mRNA–1273 [Moderna] SARS-CoV-2 vaccine.[10] The authors reported 3 participants who developed Bell palsy in the vaccine group, compared with only 1 participant in the placebo group during the observation period of the trial (>28 days after injection).[10] This seemingly small detail sparked considerable attention. Several opinion articles and case reports[4,7,8,9] have been published on the subject, and media attention has been extensive.[3,5,6,12,13] This attention could influence vaccination rates in addition to the effort of global public health in eliminating infection rates.

Previously, facial nerve palsy has been reported as a possible adverse event in other vaccinations, including influenza vaccine and meningococcal conjugate vaccine.[9,16] The mechanism for this is thought to involve the additive adjuvants that initiate an immunomodulatory response within the cells.[17] However, the mRNA-based vaccines produced by Pfizer-BioNTech and Moderna use a different mechanism without adjuvants. An immune response is nonetheless a necessary component for efficacy and, via either mimicry of host molecules or bystander activation of dormant autoreactive T cells, a theoretical association with facial nerve palsy could occur.[18] Another possibility is that the BNT162b2 vaccine might induce innate immune activation and production of interferon proteins by a combined effect of mRNA and lipids.[9] Facial nerve palsy has been reported as a possible rare complication of interferon therapy.[19]

Limitations

This study has several limitations. First, only the effects of recent vaccination were evaluated, and long-term outcomes are currently unavailable for analysis. Second, we examined only facial nerve palsy as an outcome. Third, all patients received the BNT162b2 vaccine, and results cannot be generalized to other SARS-CoV-2 vaccine types. Finally, the secondary analysis of overall patients admitted compared with preceding years could be biased by unmeasurable factors such as referral patterns.

Conclusions

In this case-control study, no association between acute facial nerve palsy and recent vaccination with the BNT162b2 vaccine was observed. In addition, despite rapid and extensive vaccination of the population, a similar volume of admissions for facial nerve palsy was seen compared with the same period in preceding years.

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Figures and Tables

Table 1.

Characteristics of Patients With New-Onset Peripheral Facial Nerve Palsy After Recent Vaccination With the BNT162b2 (Pfizer-BioNTech) Vaccine

Patient No.	Comorbidities	Laterality	HB grade[a]	Status at last follow-up
1	None	Right	IV	Partially recovered
2	None	Right	NA	Partially recovered
3	Dyslipidemia	Left	IV	NA
4	Hypertension	Left	IV	NA
5	Hypertension, prostate cancer	Left	NA	NA
6	None	Right	NA	NA
7	Cardiac pacemaker	Left	VI	Partially recovered
8	Dyslipidemia	Right	IV	NA
9	Hypertension, OSA, cochlear Ménière disease	Left	III	Partially recovered
10	None	Right	III	Partially recovered
11	None	Right	NA	Partially recovered
12	Hepatitis C	Right	NA	NA
13	Dyslipidemia, hypothyroidism, thalassemia	Right	III	NA
14	Hypertension, BPH, diabetes	Right	NA	NA
15	Asthma	Right	NA	Partially recovered
16	None	Right	II	NA
17	None	Left	III	Partially recovered
18	Small fiber neuropathy	Right	IV	Partially recovered
19	Diabetes	Right	III	NA
20	None	Left	III	NA
21	None	Left	NA	NA

Abbreviations: BPH, benign prostatic hyperplasia; HB, House-Brackmann; NA, not available; OSA, obstructive sleep apnea.

[a] Obtained at admission. Scores range from I to VI, with higher scores indicating severe nerve damage.

Table 2.

Distribution of Vaccinated and Nonvaccinated Patients Among Cases With New-Onset Peripheral Facial Nerve Palsy and Matched Controls

Patient group	No. of cases	No. of controls	Total No.
Vaccinated	21	44	65
Nonvaccinated	16	30	46
Total	37	74	111

Table 3.

Facial Nerve Palsy Cases in January and February 2021 and During the Same Period in the 6 Preceding Years

Year	No. of cases	Age, mean (SD), y	Male, No. (%)
2015	28	49.5 (17.8)	17 (60.7)
2016	26	51.4 (17.7)	17 (65.4)
2017	28	50.2 (20.8)	17 (60.7)
2018	17	52.3 (21.9)	12 (70.6)
2019	27	48.5 (21.0)	15 (55.6)
2020	35	49.2 (19.4)	23 (65.7)
2021	37	50.9 (20.2)	22 (59.5)