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Benign fasciculation syndrome and migraine aura without headache as possible adverse events after BNT162b2 mRNA vaccination: a web-based survey

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Aim To determine the characteristics of patients who experienced muscle fasciculations and migraine auras without headache after BNT162b2 immunization.

Methods In January 2022, we published a case report that described a 48-year-old female patient who experienced muscle twitching and migraine auras without headache following BNT162b2 immunization. A self-administered online survey was sent to people who had written to us and complained of similar symptoms described in the case report (N = 20).

Results The survey was completed by 11 participants, of whom 10 reported muscle twitching following BNT162b2 immunization lasting a median of 14 (4-36.5) days. Five of these participants (50%) reported migraine auras without headache. Participants further reported on self-identified triggers that altered the intensity of their symptoms, such as anxiety or caffeine. Fifty percent of participants who got an acute SARS-CoV-2 infection (3/6) experienced increased muscle symptom intensity during the acute phase of the disease.

Conclusion To the best of our knowledge, our survey is the first to summarize patients' experiences of these phenomena occurring after BNT162b2 immunization. It is important to note that no causal relationship between vaccination and these phenomena can be inferred.

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Vaccination against SARS-CoV-2 has decreased COVID-19 mortality and severe disease forms (1). Several neurological adverse events following immunization (AEFI) were reported after the BNT162b2 vaccination, but no causality could be inferred (2,3).

Benign muscle fasciculations are visible, spontaneous muscle fiber contractions that occur intermittently (3-5). Migraine aura without headache is a recurrent disorder manifesting in attacks of reversible focal neurological symptoms, neither accompanied nor followed by headache (6,7).

In January 2022, we published a case report regarding muscle twitching and migraine aura without headache in a 48-year-old woman as potential AEFI following BNT162b2 immunization. Muscle fasciculations started to intermittently appear six days after immunization. Furthermore, she experienced migraine auras with visual kaleidoscope-like phenomena on two occasions (3). Muscle twitching and migraine-related phenomena following COVID-vaccines have seldom been reported in the literature, but have been reported by laypeople on social networks (8-13).

Following the publication of our case report, we received several e-mails from people who complained of similar ailments. In this report, we aimed to summarize their experience by administering them a survey.

PATIENTS AND METHODS

This study was designed as an online self-administered survey and was approved by the Institutional Ethics Committee of the School of Medicine, University of Zagreb (380-59-10106-22-111/79). Non-probability sampling was used to select participants: people that reached out to the authors of Salai et al from 2022 (3) were sent an email in which they were asked to participate in a self-administered survey. The study design is depicted in Figure 1.

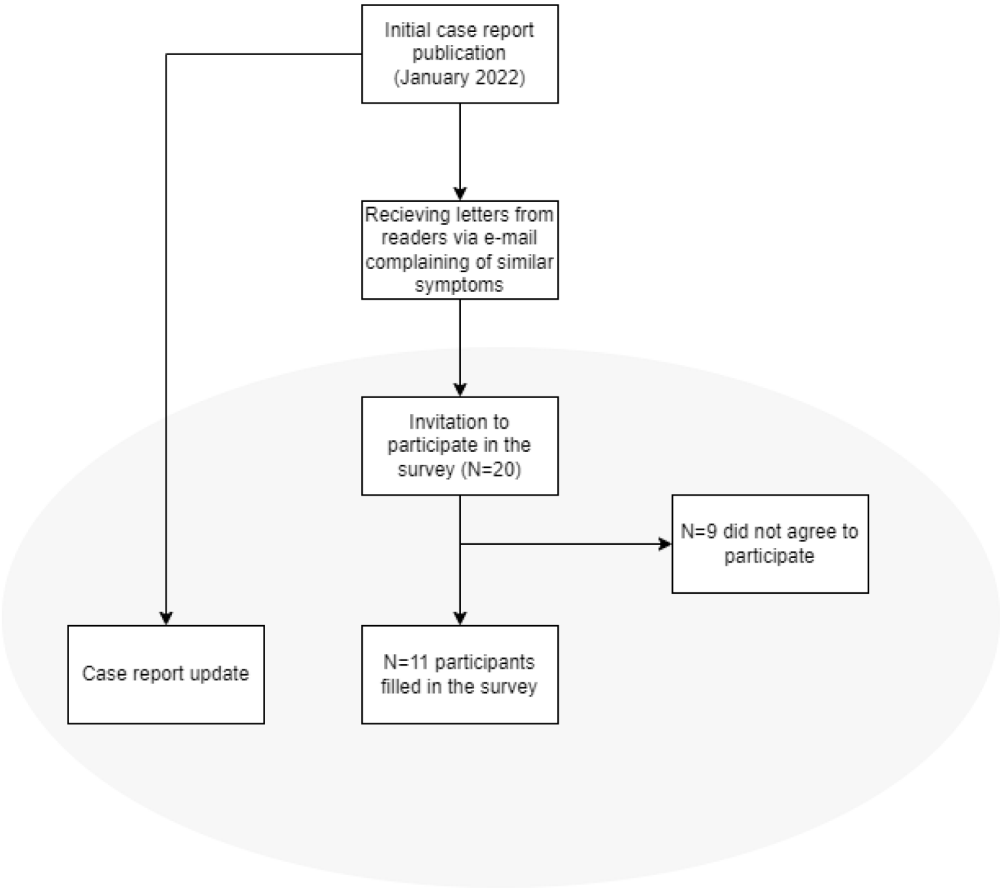

FIGURE 1. Flowchart of the study.

The survey was written in English (Supplementary Material 1) and consisted of questions regarding demographic information, twitching and/or aura symptoms, vaccination/infection status, and the EuroQoL (EQ-5D-5L) questionnaire. EQ-5D-5L was employed to quantify the participants' self-reported health using a standardized testing tool (14,15).

Qualitative variables are presented as numbers and percentages. Data normality was tested with the Kolmogorov-Smirnov test. Parametric variables are presented as mean ± standard deviation (SD); non-parametric variables are presented as median (Q1-Q3). Friedman's test was employed to assess the difference between two time points. Data analysis was conducted with MedCalc® Statistical Software, version 20.106 (16), and JAMOVI 2020 (17).

RESULTS

Case report update

After the publication of the case report (3), our patient experienced a gradual decrease in symptom intensity. In June 2022, she experienced a SARS-CoV-2 infection with mild respiratory symptoms, during which she developed worsening muscle fasciculations and had another brief episode of migraine aura. Furthermore, during the post-acute period, her fasciculations were increased for two weeks, after which the symptoms gradually decreased. Currently, she is asymptomatic.

Survey analysis

The initial invitations to participate in the survey were sent to 20 email addresses; 11 (55%) people agreed to participate (4 women). Participants' characteristics are shown in Table 1. No participant had a history of neurological illness; one had previously experienced muscle twitching, but this happened sporadically.

All participants received the BNT162b2 vaccine. The median number of doses was 2 (1-2). One participant did not ascribe muscle twitching to vaccination but to the post-acute period of SARS-CoV-2 infection. Ten participants ascribed their symptoms to immunization. Eight participants complained of AEFI after the first, and two after the second vaccination dose. In the post-vaccination phase, 10 participants experienced muscle twitching. The median time from vaccination to fasciculation onset was 14 (4-36.5) days. Five (50%) participants experienced migraine auras without headaches. All participants sought medical help for these phenomena.

The survey was filled out 321 (270-405) days after the symptom onset. Five participants stated that symptom intensity was reduced over time, 5 stated that the intensity remained the same, and 1 stated that symptoms increased in intensity. When asked to recall the level of discomfort at the time of symptom onset on a scale from 0 (no discomfort) to 10 (extreme discomfort), the median result was 9

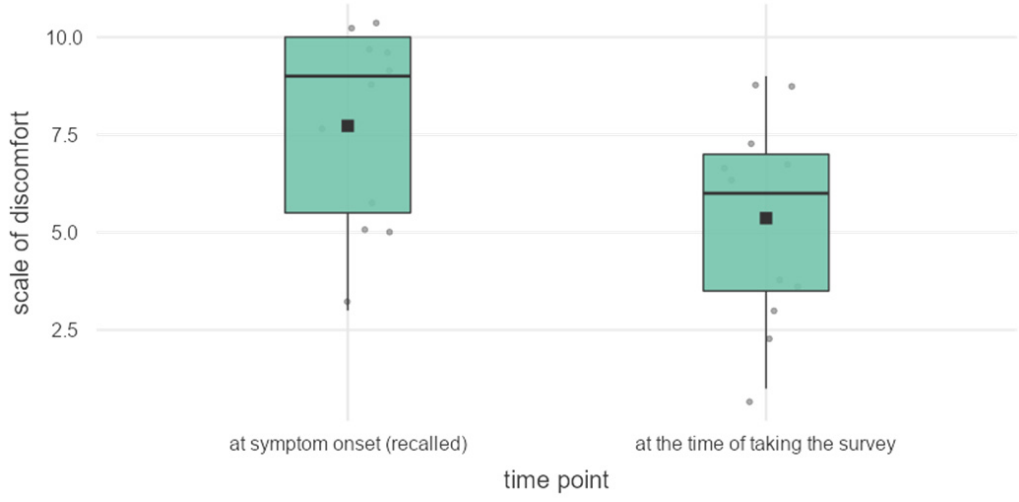

FIGURE 2. Self-assessment of overall discomfort at symptom onset (recalled) and at the time of taking the survey on a scale from 0 (no discomfort) to 10 (extreme discomfort). Black squares indicate arithmetical means.

(7-10) vs 6 (3.5-7) at the time of taking the survey ($\chi^2 = 1.6$, $P = 0.206$) (Figure 2).

TABLE 1. Participants' demographic characteristics

Participants' characteristics	N (%)
Sex	
male	7 (63.6)
female	4 (36.4)
Age (median)	32 (24.5-46)
English-speaking country	
total	10 (90.9)
Australia	3
Canada	2
United Kingdom	2
United States of America	3
Non-English-speaking country	
Austria	1 (9.1)
Healthcare workers	
total	3 (27.3)
physician	1
non-physician	2
Level of education	
high-school	2 (18.1)
bachelor's degree	5 (45.5)
master's degree	3 (27.3)
PhD	1 (9.1)
Pre-vaccination medical history	
Previous psychiatric illnesses	
anxiety	1
attention deficit hyperactivity disorder	1
none	9
Previous respiratory illnesses	
asthma	1
obstructive sleep apnea	1
none	9

When asked what factors led toward the decrease in symptom intensity, they identified the following: magnesium supplements (n = 3), physical movement (n = 1), acetazolamide (dosage unknown) (n = 1), and "vitamin supplements" (n = 1). The factors that aggravated their symptoms were caffeine (n = 2), physical exercise (n = 2), and anxiety and emotional stress (n = 2).

Six participants had a SARS-CoV-2 infection, of whom 3 experienced muscle twitching during acute infection. Participants tested positive after a median of 270 (205-294) days after receiving the dose after which they noticed AEFIs. None experienced migraine auras during acute infection. Nine participants filled in the EuroQoL-5D-5L portion of the survey (Table 2). Problems across five standardized dimensions were either slight or moderate. All participants reported problems in the "pain/discomfort" dimension. When asked how good or bad their health was today, the median response was 75 (50-80) out of maximum 100.

DISCUSSION

We conducted a non-probability sampling-based online survey aiming to further explore muscle fasciculations and migraine auras as potential AEFI. Our survey indicated a non-significant decrease in self-assessed discomfort level at the time of taking the survey compared with the recalled discomfort level at the time of symptom onset. A half of the participants who had SARS-CoV-2 infection after vaccination experienced increased muscle twitching, and the same was true for the patient we presented in our original case report. Muscle fasciculations have previously been described to occur during acute COVID-19 (18). Furthermore, in a telephone interview-based study of patients

TABLE 2. EuroQoL-5D-5L questionnaire results, reported as the number of participants per dimension per level and as percentage (based on a number of participants who completed the questionnaire)

	Mobility N (%)	Self-care N (%)	Usual activities N (%)	Pain/discomfort N (%)	Anxiety/depression N (%)
Level 1 No problems	6 (66.6)	9 (100)	3 (33.3)	0	4 (44.4)
Level 2 Slight problems	1 (11.1)	0	5 (55.5)	3 (33.3)	2 (22.2)
Level 3 Moderate problems	2 (22.2)	0	1 (11.1)	6 (66.6)	3 (33.3)
Level 4 Severe problems	0	0	0	0	0
Level 5 Unable to do	0	0	0	0	0
Complete data	9	9	9	9	9
Missing data	2	2	2	2	2
Total	11	11	11	11	11

with previously diagnosed benign fasciculation syndrome (BFS), a subset of patients self-reported exacerbation of symptoms during acute viral infections (19). It has been hypothesized that viral infections might impact the course of BFS by triggering autoimmunity (20-22). Muscle spasms after vaccination are generally considered to be mild and self-limiting AEFI (23,24). While BFS may be uncomfortable and present a high psychological burden, its disease course is benign (25).

Our study has several major limitations. First, it was based on a self-administered online survey and is prone to self-reporting bias (26); additionally, no objective clinical measurements were employed. Second, we used non-probability sampling, enrolling people who sent us an e-mail, usually because they found similarity between the symptoms we previously described (3) and the phenomena they experienced, which makes this study additionally prone to sampling bias (27). Besides this, our previous case report was in English, so the accessibility to it, as well as the ability to contact the authors, was limited to English speakers. Furthermore, the study had a small sample size and lacked a control group (which is inherent to our study design). An important point to consider is also the bidirectional relationship between health anxiety and BFS (5,28), as it is possible that searching for information of muscle fasciculation could exacerbate the symptoms. Finally, the potential impact of SARS-CoV-2 infection on muscle fasciculation in our study participants might be a source of confounding when assessing symptom severity.

To conclude, we reported a summarized experience of a small subset of people who had read our previous report and decided to contact us (most likely) due to the similarity with their own condition. It is very important to highlight that no causal inference can be made regarding BNT162b2 vaccination and muscle fasciculations or migraine auras without headache. The primary intention of our study was to report the presence of individuals who had experienced similar phenomena as our patient. To emphasize, muscle twitching and/or migraine auras without headaches that occur following SARS-CoV-2 vaccination seem to be extremely rare events: clinical studies with systematical and objective measurements are required in order to elucidate the potential relationship between BNT162b2 vaccination and these phenomena in certain individuals.

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Declaration of authorship GS, LG conceived and designed the study; GS, DLJ, RN acquired the data; all authors analyzed and interpreted the data; GS drafted the manuscript; DLJ, RN, LG critically reviewed the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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