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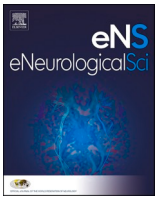

Clinical characteristics of motor functional neurological disorder manifesting as limb weakness after vaccination against coronavirus disease 2019: A case series

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ABSTRACT

Background: The characteristics of functional limb weakness (FLW) as one of the manifestations of functional neurological disorder after vaccination against coronavirus disease 2019 (COVID-19) remain controversial.
Methods: In this descriptive case series, we aimed to elucidate the characteristics of Japanese patients with FLW who claimed muscle weakness after COVID-19 vaccination among patients who visited our outpatient clinic between 1 June 2021 and 31 December 2022.
Results: Nine patients were diagnosed with FLW (mean age: 30.8 years), including two men and seven women. Seven patients were vaccinated with the BioNTech/Pfizer vaccine and two with the mRNA-1273 Moderna vaccine. All patients demonstrated various positive signs for FLW. Magnetic resonance imaging or computed tomography indicated no abnormality that could explain their symptoms. At the time of the clinic visit, five patients were treated for psychiatric disorders, including depression, insomnia, attention-deficit hyperactivity disorder, and Asperger's syndrome. Muscle weakness spread to the limbs beyond the vaccinated arm in seven patients.
Conclusions: We describe the basic characteristics of FLW in Japanese patients after COVID-19 vaccination. Further recognition of these characteristics could aid the diagnosis of FLW by physicians allowing them to support these patients effectively.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), led to a global pandemic, and several vaccines have been developed to protect against COVID-19. Two mRNA vaccines, the BNT162b2 mRNA COVID-19 vaccine (BioNTech/Pfizer) and the mRNA-1273 COVID-19 vaccine (Moderna) had been administered to 81% of the Japanese population as of 7 June 2023. [1] Both vaccines have been confirmed to be effective, and governments around the world have been striving to facilitate vaccination among their people for the last few years. [2,3] The hesitancy or reluctance to undergo vaccination has been discussed as one of the factors contributing to the spread of infections such as COVID-19 and the consequent jeopardy to public health. [3–5] This hesitancy or reluctance is thought to be triggered by various factors, including concerns over the side effects of vaccines among the public. [6,7] Thus far, the benefits of COVID-19 vaccines have been proven to outweigh the risks, and more accurate and detailed information about their side effects is expected to improve acceptance and reduce hesitancy. The side effects of COVID-19 vaccines include local injection site reactions, fever, fatigue, and various neurological conditions (such as headache, venous sinus thrombosis, encephalitis, epilepsy, Guillain-Barre syndrome, facial palsy, myositis, and dermatomyositis). [8–11]

Functional neurological disorders (FNDs), characterized by disruptive and disabling neurological symptoms of unknown pathophysiology, have been recognized as a common cause of neurological disability.

Abbreviations: COVID-19, coronavirus disease 2019; FND, functional neurological disorders; FLW, functional limb weakness; DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MRI, magnetic resonance imaging.

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[12,13] Patients with FNDs show various symptoms, including weakness, tremor, gait disturbance, and non-motor symptoms (such as sensory disturbance, fatigue, or functional seizures), and viral infections and vaccines have been recognized as potential triggers of FNDs. [13] After the COVID-19 pandemic set in, society was placed under great pressure, partly as a result of the uncertainty around people's mental health, with previous studies describing an increase in FND consultations. [14] Currently, FNDs are known to have several manifestations, including functional seizures (also called dissociative or psychogenic non-epileptic seizures), functional movement disorders, including functional limb weakness (FLW), chronic dizziness, and cognitive dysfunction. [13,15] Although FNDs were reported to have general geographic data, such as age and female predominance, [16–19] some subtypes might have different tendencies in terms of sex predominance. [19] Thus, FNDs might be heterogeneous, with each subtype having different tendencies in terms of medical variables. Relationships between COVID-19 vaccines and FNDs have been reported previously, but few studies have analyzed these relationships while considering the heterogenicity of FNDs. [20,21]

After June 2021, we began to recognize the longstanding symptoms of patients with COVID-19, termed long COVID, and those vaccinated against COVID-19 at the National Center of Neurology and Psychiatry National Center Hospital, Japan. [22,23] The basic geographical characteristics of Japanese patients with long COVID were reported based on retrospective data analyses. [23] At the clinic, we have cared for patients with various alleged longstanding symptoms after COVID-19 vaccination, particularly FLW. In this study, we report the characteristics of a series of patients with FLW. This single-center study was conducted to exclude ambiguity due to the heterogeneity of the characteristics of FNDs, and the medical features of FLW were analyzed using consistent measures.

2. Patients and methods

We performed a single-center retrospective review at the Department of General Internal Medicine of the National Center of Neurology and Psychiatry, Japan. The electronic medical records of patients who visited the clinic from 1 June 2021 to 31 December 2022 were examined. FNDs and FLW were diagnosed by neurological experts (M.O. and M.T.) based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), accompanied by at least one positive motor sign indicating FNDs. [24] All patients were aged over 15 years and had undergone at least one dose of the BNT162b2 mRNA COVID-19 vaccine (BioNTech/Pfizer) or the mRNA-1273 COVID-19 vaccine (Moderna) before their visit. Demographic data, the results of clinical examinations, and the imaging test results were collected from the patients' medical records.

Brain magnetic resonance imaging (MRI) was performed using a 3.0-T scanner with T1-weighted, T2-weighted, diffusion-weighted, and susceptibility-weighted imaging, as well as fluid-attenuated inversion recovery. Additional tests, including electromyography and nerve conduction assessments, were performed at each examiner's discretion.

3. Results

3.1. Patients' demographic characteristics

Nine patients (two males and seven females) were included in this study and claimed continuous or fluctuating muscle weakness, which allegedly started after COVID-19 vaccination (Table 1). All nine patients had not been previously infected with COVID-19. Seven patients received the BioNTech/Pfizer vaccine and two received the Moderna vaccine. The mean age of the patients was 30.7 years. One patient could not recall the exact date of their last vaccine dose (Case 6), but she affirmed that at least 5 months had passed since the last dose at the time of the first visit to our clinic. During follow-up at the clinic, four patients demonstrated an improvement in symptoms. The average number of days between the other seven patients' last vaccine doses and their first visit to our clinic was 155 days, and the shortest duration was 54 days (Table 2). Before vaccination, five patients had been diagnosed with psychiatric disorders, including attention-deficit hyperactivity disorder (ADHD), Asperger's syndrome, adjustment disorder, and depression. When limb weakness was first noticed, two of the five patients were taking medicine for their psychiatric disorders: one patient with ADHD was taking atomoxetine hydrochloride 30 mg per day and another was taking paroxetine hydrochloride 10 mg, risperidone 1 mg, and triazolam 0.25 mg per day. These medications were taken continuously by these patients before and after the symptoms started. We confirmed no other

Table 1
Cases of functional motor disorder following vaccination against COVID-19 in the clinic.

Case No.	Age (years)/ sex	Vaccine, doses	Latency to onset	Duration between vaccination and visit (days)	Clinical features	Positive signs	SARS-CoV-2 anti-spike antibody (U/mL)	Course of alleged symptoms
1	39/F	P, 1	3 days	109	Fluctuating limb weakness, paresthesia, pain, leg jerks	Co, Abd	34.3	Improved 2 years after the first visit
2	23/F	P, 2	Just after vaccination	58	Single upper-limb weakness and numbness	Co, PW	577	Improved 3 months after the first visit
3	24/M	Mo, 2	2 days	170	Single upper-limb weakness	Co, PW	N/A	Improved at the first visit
4	16/M	P, 2	3 days	154	Single upper-limb weakness	Co, PW	N/A	No change at the first visit
5	35/F	P, 1	Just after vaccination	128	Single upper-limb weakness and numbness	PW	N/A	Improved 1 month after the first visit
6	59/F	P, 2	30 days	Approximately 5 months	Single lower-limb weakness and numbness	Co, Abd, PW	355	No change until 1 month after the first visit
7	29/F	P, 2	20 days	319	Single-sided upper- and lower-limb weakness and fatigue	Co, Abd, PW	11,400	No change until 1 month after the first visit
8	31/F	P, 1	Just after vaccination	248	Single upper-limb weakness	PW	N/A	No change until 1 month after the first visit
9	21/F	Mo, 3	2 weeks	54	Four-limb weakness, fatigue, and headache	Co, Abd, PW	N/A	Improved 1 month after the first visit

F: female; M: male; P: BioNTech/Pfizer BNT162b2 vaccine; Mo: Moderna mRNA-1273 vaccine; Co: collapsing/give-way weakness; Abd: abductor sign; MI: motor inconsistency; PW: paradoxical wrist flexion; N/A: not applicable.

Table 2
Basic demographic characteristics of patients included in the study with long-standing muscle weakness after COVID-19 vaccination.

Number of patients (male/female)	9 (2/7)
Mean age, years	30.8
Race, Asian	9
Mean number of days from the last vaccination	155
Vaccine with which patients were vaccinated	
Pfizer	7
Moderna	2
Number of patients who were vaccinated with the first, second, and third doses	
First	3
Second	5
Third	1

medications were used by the other seven patients.

3.2. Presenting symptoms

Symptom onset occurred immediately after vaccination in three patients, within a few days in three patients, and after 2 weeks in three patients. All patients claimed limb weakness, and six showed weakness spreading to limbs other than the vaccinated limb. Two patients claimed limb weakness in the opposite limb without normal muscle strength on the vaccinated side. One patient experienced temporary lower-limb weakness on the same side as the vaccinated arm. The degree of muscle weakness was mild—Medical Research Council (MRC) grade 4/5 in eight cases and one other patient, Case No. 8, was MRC grade 0/5 without muscle atrophy. When the patients visited the clinic, the affected limb was the vaccinated arm in six cases, the opposite arm in four cases, the leg on the same side in three cases, and the opposite leg in two cases (Table 3). All patients claimed fluctuations in their symptoms according to their medical history. Regarding accompanying symptoms, pain or numbness in the limbs was found in four patients, fatigue in two patients, and headache in one patient. A diagnosis of FND in all patients was made based on the DSM-5 diagnostic criteria, and all patients had at least one "rule-in" neurological examination sign, [25] including the abductor sign [26] in four patients, give-way weakness [27] in seven patients, motor inconsistency [28] in two patients, and paradoxical wrist flexion [29] in eight patients (Table 4). Four of the nine patients were followed at the clinic after their first visit, and it was confirmed that limb weakness improved in these patients.

3.3. Examination findings

Brain MRI was performed in eight patients and brain computed tomography (CT) in one patient. In addition, cervical MRI was performed in six patients and lumbar MRI in one patient. The images showed no abnormalities indicative of other diseases, such as old cerebral infarction, multiple sclerosis, or cervical spondylosis, that could explain their weakness. Either electromyography or nerve conduction assessment was conducted in five patients, and no abnormality was identified. Blood tests were performed in four patients, and no significant abnormality was identified, which suggests that another structural disease was confirmed. In the four patients who underwent blood tests, SARS-CoV-2 antibodies were checked using the Elecsys® Anti-SARS-CoV-2 S assay (Roche Diagnostics Int., Rotkreuz, Switzerland), and these patients showed an anti-spike-positive and anti-nucleocapsid-negative serological response, which is compatible with vaccine-induced immunization. [30] The anti-spike antibody concentration ranged from 34.3 to 11,400 U/mL (Table 1). Therefore, no structural disease that could explain limb weakness was found in any patient.

Table 3
Summary of alleged symptoms in patients with FND.

Location of muscle weakness (total of 10 patients)	
Vaccinated upper limb	6
Opposite upper limb	4
Lower limb on the same side	3
Lower limb on the opposite side	2
Limited within the vaccinated upper limb	1
Other symptoms	
Fatigue	2
Headache	1
Pain/numbness	4

FND, functional neurological disorders.

Table 4
Summary of positive findings for FND diagnosis.

Manifestation	Number of patients
Collapsing/give-way weakness	7
Hip abductor sign	4
Motor inconsistency	2
Paradoxical wrist flexion	8

FND, functional neurological disorders.

4. Discussion

The most effective prevention measure against COVID-19 is vaccination, and several vaccines are now available worldwide. The BioNTech/Pfizer and Moderna vaccines are the most commonly used in Japan, and there is no clear evidence that these vaccines increase adverse events. [10] As mRNA-based double-dose vaccines, the BioNTech/Pfizer and Moderna vaccines are associated with local and systemic reactions, which decline markedly through day 7 after injection. [31] In Japan, fatigue, muscle pain, and fever are common side effects of the BioNTech/Pfizer vaccine, and these side effects were reported to diminish within 1 week. [32] Other various neurosurgical symptoms have been described as possible side effects of COVID-19 vaccines, but the causal relationships between these side effects and the vaccines are unclear. [33] To the best of our knowledge, no reports have analyzed longstanding (over several months) symptoms that allegedly started after vaccination. This study is the first to elucidate such symptoms that were sustained for at least 2 months through homogeneous and consistent examination at a single medical center.

We reported longstanding weakness in patients with FLW after vaccination against COVID-19. Some case reports have shown FNDs after vaccination, but most symptoms disappeared or improved over a short period after vaccination with fluctuations to some extent. [34] Another study reported symptoms that persisted over several months. [35] In addition to the positive objective signs of FNDs, the patients in the present case series were likely to have several characteristic features, including female predominance, young or middle age, and fluctuation and spreading of symptoms. [20,36] Our findings clarify that FLW after COVID-19 vaccination has some features that could be valuable when assessing a positive diagnosis of FNDs, which might help general physicians avoid misdiagnosing FLW as another organic disease. Past case reports reported that some FND symptoms spread to parts of the body other than the vaccinated arm and fluctuated after COVID-19 vaccination [35,36]. In this study, the symptoms of most patients with FLW fluctuated and spread to other limbs, which were common characteristics. Fluctuations in, and spreading of, these symptoms contributed to the correct and timely recognition of FLW after vaccination in addition to the already known geographical characteristics of female dominance and young or middle age. A correct diagnosis supported by these findings is crucial to help build confidence in people who are hesitant to undergo vaccination, as well as improving global public health in relation to COVID-19.

In this study, we focused on FLW as a presentation of FNDs, which thus far has not been reported. The DSM-5 requires positive signs for an FND diagnosis, and identifying stressors is no longer necessary. [24] The

DSM-5 enables neurologists to make a diagnosis based not only on an exclusive diagnosis, but also on several positive signs, such as Hoover's sign, with which neurologists are familiar. In addition, FNDs have heterogeneous clinical symptoms and might have various etiologies. Therefore, to achieve the correct FND diagnosis and avoid the known heterogeneity of FNDs, we focused solely on FLW in this study. This study design enabled us to conclude that the findings in this report were likely to be specific to FNDs.

In this study, the diagnosis of FLW was based on positive neurological signs and the confirmation of no abnormality on head MRI or CT, in addition to medical history and neurological assessments. In some patients, positive anti-spike protein antibody with an anti-spike-positive and anti-nucleocapsid-negative serological response helped to exclude the possibility of long COVID, of which one of the symptoms is limb weakness. [37] FNDs were not diagnosed by exclusion, but based on supportive findings, such as the presence of the abductor sign, give-way weakness, motor inconsistency, and paradoxical wrist flexion. [26–29] Stressor identification is no longer an essential element for FND diagnosis. Instead, the confirmation of positive neurological signs that allow the reliable distinction of FNDs from other similar presentations is required. [13] In most patients in this study, we confirmed multiple positive neurological signs in each patient, and paradoxical wrist flexion was the most common among these signs. Its sensitivity and specificity were reported as 67% and 100%, respectively, [29] and the high positive rate of this sign might support the validity of the FND diagnosis. Because stressors have been omitted as an FND diagnostic criteria in the DSM-5, stressors were not analyzed in this study; however, the COVID-19 pandemic was accompanied by various restrictions in daily life, which might have been major stressors for patients. Under the circumstance of vaccination against COVID-19, the existence of stressors might have had less of an impact on the FND diagnosis in this study.

Another point to note is that this study focused on FND development after COVID-19 vaccination. FNDs were reported in patients who were vaccinated against other pathogenic conditions, such as human papillomavirus and H1N1 influenza. [38–40] For example, symptoms after mass vaccination against pandemic influenza A (H1N1) in South Korea included weakness of limbs other than the arm in which the vaccine was administered, with female predominance. [40] This feature was observed in the present study; thus, FND development after vaccination, especially in subtypes with FLW, might be common among various types of vaccine.

This study had several limitations that should be noted. This was a single-center, retrospective study with a relatively small sample size and no control group. Moreover, all of the patients were vaccinated with the BioNTech/Pfizer or Moderna vaccines, and none of the patients received other vaccines that may be used in other countries.

5. Conclusion

In this study, we reported the basic characteristics of FLW as one manifestation of FNDs in patients after COVID-19 vaccination. We confirmed several characteristics among these patients and emphasized the importance of diagnosing FNDs after COVID-19 vaccination to treat patients who suffer from longstanding symptoms and to effectively support these patients by achieving a correct early diagnosis.

Ethics statement

The protocol was approved by the NCNP Clinical Research Review Committee (No. A2021-101).

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CRediT authorship contribution statement

Masayuki Ohira: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Takashi Osada:** Writing – review & editing, Supervision, Data curation. **Hiroaki Kimura:** Writing – review & editing, Supervision, Data curation. **Terunori Sano:** Writing – review & editing, Supervision, Data curation. **Masaki Takao:** Writing – review & editing, Supervision, Funding acquisition, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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