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**Citation for published version:**

Butler, M, Coebergh, J, Safavi, F, Carson, A, Hallett, M, Michael, B, Pollak, TA, Solomon, T, Stone, J & Nicholson, TR 2021, 'Functional Neurological Disorder After SARS-CoV-2 Vaccines: Two Case Reports and Discussion of Potential Public Health Implications', *Journal of Neuropsychiatry and Clinical Neurosciences*, pp. appi.neuropsych. <https://doi.org/10.1176/appi.neuropsych.21050116>

**Digital Object Identifier (DOI):**

[10.1176/appi.neuropsych.21050116](https://doi.org/10.1176/appi.neuropsych.21050116)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Journal of Neuropsychiatry and Clinical Neurosciences

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## Functional Neurological Disorder After SARS-CoV-2 Vaccines: Two Case Reports and Discussion of Potential Public Health Implications

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Dr. Butler is a National Institutes of Health Research (NIHR) Academic Clinical Fellow (grant ACF-2019-17-008). Drs. Safavi and Hallett are supported by the Division of Intramural Research, the National Institute of Neurological Disorders and Stroke, and NIH. Dr. Michael is supported to conduct COVID-19 neuroscience research by the United Kingdom Research and Innovation/Medical Research Council (MRC) (grant MR/V03605X/1); and he receives research grant support from MRC/UKRI (grant MR/V007181/1), MRC (grant MR/To28750/1), and Wellcome (grant ISSF201902/3). Dr. Solomon is supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (grants IS-HPU-1112-10117 and NIHR200907), NIHR Programme Grant for Applied Research (grant RP-PG-0108-10,048), NIHR Global Health Research Group on Brain Infections (grant 17/63/110), and the European Union's Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America Network; grant 734584.) Dr. Pollak is supported by an NIHR Clinical Lectureship. The other authors report no financial relationships with commercial interests.

The authors thank Dr. Avindra Nath for his support with one of the cases in this article.

The funding agencies had no role in the preparation of this article or in the decision to submit it for publication.

The authors have confirmed that details of the cases have been disguised to protect patient privacy.

## INTRODUCTION

The scientific community responded rapidly to the COVID-19 pandemic by developing novel SARS-CoV-2 vaccines that have been shown to be safe and effective (1). Global vaccination programs have been rolled out with variable progress (2). Some vaccines have been suspended for certain demographic groups in a number of countries as a result of rare associations with cerebral venous sinus thromboses (3). Vaccine programs are dependent on public trust, which may be affected by safety concerns and vaccine hesitancy, both of which can be fueled by misinformation (4).

Transient neuropsychiatric side effects of SARS-CoV-2 vaccines, such as headache and fatigue, have been reported in low numbers (<5%) in clinical trials. However, there have been sporadic reports of more serious neurological disorders, including facial paralysis (Bell's palsy), at low rates with both Pfizer-BioNTech (N=4/21,823 in the vaccinated group versus N=0/21,828 in the placebo group) (1) and Moderna (N=3/15,210 in the vaccinated group versus N=1/15,210 in the placebo group) vaccines (5), although these rates are consistent with the baseline population prevalence of 30–40 per 100,000 (6).

Likewise, postlicensing, the majority of reported serious allergic events in response to COVID-19 vaccines have not been validated: rates of confirmed anaphylaxis are low (7), and there have been no additional confirmed associations between vaccine administration and any severe neurological adverse events (8). Despite this, over recent weeks, a number of videos have been widely shared on social media and some news channels reporting severe neurological adverse events from COVID-19 vaccines. These videos have led to understandable public concerns, but after review by the medical directors of the Functional Neurological Disorder (FND) Society, these adverse events seem to have clinical features suggestive of FND (9–11). Previous similar media videos of seizures and movement disorders have been reliably diagnosed as FND by remote expert assessments (12).

It is recognized that some acute responses to vaccinations do not have an immunological cause and are not directly related to the vaccine constituents. Accordingly, the World Health Organization (WHO) recognizes immunization stress-related responses (ISRRs) as a disqualifier in causality assessment of an adverse event following immunization. These ISRRs include but are not limited to acute stress responses, vasovagal reactions, and dissociative (synonymous with functional) symptoms (13). In our opinion, neurological ISRRs best refer to FND subtypes that are specifically triggered by vaccines. These are most commonly transient and mild but can be severe and potentially longer-lasting.

Understanding of FND has developed dramatically in the past decade. Older conceptions of FND have been replaced by more nuanced, biopsychosocial models that while acknowledging the important role of stress, do not assume its relevance for all individuals, and instead focus on cognitive and neurobiological processes underpinning symptom formation and persistence. Indeed, stressor identification is no longer an essential diagnostic criterion and has been replaced by the requirement to identify positive neurological signs that allow the reliable distinction of FND from other similar presentations (14).

Here, we present two cases of probable FND precipitated by the administration of a SARS-CoV-2 vaccine. Written informed consent was obtained from both patients.

## CASE REPORTS

### Case One

A 38-year-old female with no significant past medical history was administered the first dose of the Pfizer-BioNTech SARS-CoV-2 vaccine to her left arm. Around 20 minutes postvaccination, she developed an odd sensation (which the patient described as “weakness”) around the left ear, which in seconds spread to the mouth and then to the left arm and leg over the rest of the day. No headache or other symptom was noted.

On waking the next morning, the patient had difficulty moving the left side of her face, as well as heaviness in her left leg. Her general practitioner called an ambulance; the emergency department consultant and stroke team documented mild left-sided arm weakness in the distal muscles and forearm (score of 4 on the Medical Research Council [MRC] Scale for Muscle Strength, indicating movement against gravity and resistance [scale range: “0”=no visible contraction to 5=normal]), downward deviation of the angle of the mouth on the left (without change to the eyelid), and tongue deviation to the right. The patient noted left-leg heaviness, but an MRC scale score of 5 was documented for the leg, and no comment was made of any gait abnormality. The patient had normal blood pressure, glucose level, and heart rate, and an electrocardiogram and computerized tomography scan of her brain were normal. She was discharged from the emergency department with a working diagnosis of either a transient ischemic attack or Bell’s palsy, and was started on aspirin (75 mg once a day).

The patient’s difficulty in moving her left arm and left leg, as well as her facial weakness, continued and peaked 2 days after the vaccine was administered. When she was seen at the stroke clinic 1 week later, she had ongoing left-sided weakness on examination. She also reported new and ongoing intermittent word-finding difficulty and stammering (without dysarthria), which started a few days after the initial event and worsened when she was tired. An MRI brain scan at the stroke clinic appointment, including diffusion-weighted imaging, was normal. She was discharged from the stroke clinic for follow-up in a general neurology clinic.

Two months postvaccination, the patient was examined in a general neurology clinic by a neurologist (J.C.). She had ongoing left-sided weakness, particularly in grip strength, although the weakness had gradually (albeit variably) improved over the preceding few weeks. She also reported ongoing difficulties with short-term memory (e.g., losing track of conversations or misremembering why she came into a room). The only abnormality on neurological examination was mild weakness in the left lower limb with positive hip abductor and Hoover’s sign. FND was diagnosed on the basis of positive neurological measures, including Hoover’s sign, hip abduction test, and symptom variability. These results were explained and demonstrated to the patient.

### Case Two

A 36-year-old woman with no significant past medical history received the first dose of Moderna SARS-CoV-2 vaccine in her right arm without any noticeable side effects except a sore arm. Four weeks later, she received the second dose in her right arm, and a few minutes afterward noted weakness in her right hand and new right-leg limping, which lasted for about 2 hours. Associated fatigue, myalgia, and self-reported low-grade fever subsided within a day; however, she noticed severe bilateral leg heaviness and difficulties in fine movements of the right hand on the second day postimmunization. Additionally, she had exertional fatigue after walking short distances. After several days of these symptoms, she sought medical attention.

On examination, the patient was noted to have right upper-extremity weakness and was not able to lift either leg in either sitting or supine positions. MRI of the brain and spine were normal, as were electromyography and nerve conduction velocity studies. Upon further examination by a neurologist, she was noted to have mild weakness (MRC scale score  $\geq 4$ ) in the right upper and lower limbs, but her reflexes and sensory examination were normal.

The patient started physical therapy that resulted in improvement of her right-sided weakness. Despite this, a few weeks later, she awoke with new-onset left-sided upper and lower limb weakness. Repeat cervical spine MRI was unremarkable. She continued physical therapy on the recommendation of her doctors. During evaluation by two neurologists (M.H. and F.S.) 7 weeks from the second vaccination, she reported fluctuation in her left- and right-sided weakness, as well as tightness and heaviness in her neck extensors. Additionally, she reported difficulty in performing her routine activities of daily living and tolerating any exertions above the limited isometric exercises during physical therapy.

On examination, the patient had an MRC scale score of 5 for all limbs; however, at times she found it difficult to move them. Hoover's sign was positive in the right leg, and giveaway weakness was noted in several muscle groups. Although she complained of rapid muscle fatigue, she was able to hold a one-pound weight for several minutes. She demonstrated low-amplitude rapid postural tremor in both hands, with the appearance of an enhanced physiological tremor. Her reflexes were normal. While walking, she dragged her right foot with no arm swing on the right side, but when asked to run, she moved both arms and legs symmetrically. She was diagnosed with functional weakness, tremor likely due to anxiety, and fatigue symptoms similar to those of chronic fatigue syndrome.

## DISCUSSION

Here, we described two previously healthy people who developed probable FND after receiving a SARS-CoV-2 vaccine. FND is a common condition that can lead to distressing and disabling symptoms, which can resemble almost any form of neurological symptoms; common FND subtypes are seizures, paralysis, and movement disorders, often with associated sensory and cognitive symptoms. Although there is no structural neurological lesion identified in FND, it is a consequence of disordered neurological function (14).

In some cases, childhood adversity and psychological stress can be relevant risk factors in the development of FND; however, in many cases these are not present or are only a small part of the overall picture (15). FND is now instead diagnosed via the presence of positive neurological signs (e.g., Hoover's sign). Clinicians require experience in recognizing FND to make a firm diagnosis and explain the nature of the disorder to patients, who may be baffled by their diagnosis and symptoms (16).

It is recognized that some acute responses to vaccinations mimic symptoms of allergic reaction or anaphylaxis, such as panic, collapse, and laryngeal dystonia, which do not have an immunological cause and are not directly related to the vaccine constituents (17). As well as this, human papillomavirus vaccinations in Brazil have precipitated functional seizures (18), and there have been reported cases of FND following the H1N1 (Swine 'flu) vaccination in Taiwan (19) and South Korea (20). In both Taiwan and South Korea, these symptoms predominantly affected schoolchildren; in some cases in Taiwan, symptoms of functional dizziness and weakness spread in clusters of mass psychogenic (functional) illness, all of which resolved without medical

intervention (21). This phenomenon has been echoed in multiple other countries and in response to different vaccines (16, 22). Inappropriate management of these adverse events could be disruptive to vaccination programs, and vaccine providers should have training in recognizing these disorders, which should be treated differently than, for example, allergic reactions.

Pandemic-related factors which are implicated in increased risk of developing functional symptoms in response to vaccination include, but are not limited to, pandemic stress and feelings of uncertainty about SARS-CoV-2 vaccinations (9). In many cases, FND is precipitated by physical disorders, sometimes superficially minor injuries or accidents (23). In the case of vaccination, it is plausible that physiological reactions (e.g., vasovagal or flu-like symptoms), as well as pain from the injection site, may trigger or evolve into functional symptoms (11, 24).

It is important that clinicians are able to recognize FND reactions to COVID-19 vaccines for two principal reasons. First, early recognition of such reactions is essential because it increases the chances of symptom improvement with evidence-based treatment. This includes explanation of FND (25), as well as demonstration of positive signs (26). In addition, it may prevent the patient from missing out on further multidisciplinary treatment for FND, where necessary (14). Second, recognizing FND reactions early can help to ensure that public perception of neurological adverse events triggered by the vaccines is not damaged by misinformation, which is easily spread by a globally interconnected social media. It is more likely that patients might resort to other explanations at odds with scientific understanding, such as antivaccination theories, to explain their symptoms if they feel dismissed by clinicians.

Finally, the above cases highlight the importance of using positive signs (seen in both cases and in videos on social media [9]) to diagnose FND and distinguish this disorder from other neurological disorders. This is in contrast to current WHO recommendations advising that ISRRs are diagnoses of exclusion (13). We recommend that guidelines be brought in line with contemporary diagnostic criteria for FND, which, alongside terminology and linked explanatory models preferred by patients, are often the basis of successful management (14).

A limitation of the first case report is the initial uncertainty in diagnosis. There was no documentation of positive signs at the time of initial presentation, although these were present when reviewed by a neurologist. We consider FND to be the most likely explanation.

## **CONCLUSIONS**

In summary, two cases of FND were precipitated by administration of a SARS-CoV-2 vaccine. These cases highlight that FND is likely to arise in multiple cases within the large-scale SARS-CoV-2 vaccination program and should be considered as a differential diagnosis when assessing post-vaccine neurological symptoms. It is hoped that informing the public about the occurrence of FND, which is real and disabling but does not implicate any vaccine constituents, will help ongoing uptake in the SARS-CoV-2 vaccination program.

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