Brief report (max. 2000 words; currently 1993 without summary)

**Functional neurological disorder after SARS-CoV-2 vaccines: two case reports and discussion of potential public health implications**

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**Summary (100 words – currently 92)**

Although transient mild adverse effects following SARS-CoV-2 vaccines are common, serious events are extremely rare. There have been reports on social and other media of severe neurological reactions to SARS-CoV-2 vaccines resembling functional neurological disorder (FND), but these are not confirmed or published. We present two cases of FND occurring after a SARS-CoV-2 vaccination. Understanding that FND is common, can be triggered by vaccinations and diagnosed with positive clinical signs differentiating it from other conditions will optimise management of cases that could otherwise fuel vaccine safety concerns with detrimental public health impacts.

**Introduction**

The scientific community responded rapidly to the COVID-19 pandemic by developing novel SARS-CoV-2 vaccines which have been shown to be safe and effective.1 Global vaccination programmes have been rolled out with variable progress.2 Currently, the AstraZeneca vaccine in suspended for certain groups in a number of countries due to rare associations with cerebral venous sinus thromboses.3 Vaccine programmes are dependent on public trust, which may be impacted by safety concerns and ‘vaccine hesitancy’ which can be fuelled by misinformation.4

Transient neuropsychiatric side effects to SARS-CoV-2 vaccines, such as headache and fatigue, have been reported in low numbers (<5%) in clinical trials. There have been sporadic reports of more serious neurological disorders, including facial paralysis (Bell’s palsy), at low levels in both Pfizer-BioNTech (4/21,823 in vaccine group versus 0/21,828 in placebo group)1 and Moderna vaccines (3/15,210 in vaccination groups versus 1/15,210 in placebo group)5 although these rates are consistent with baseline population prevalence of 30-40/100,000.6

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

It is recognised 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 Organisation (WHO) recognise ‘immunisation stress related responses’ (ISRR) as a disqualifier in their ‘causality assessment of an adverse event following immunization’ tool.13 These ISRR 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 specifically triggered by vaccines that are most commonly transient and mild, but can be severe and potentially longer lasting.

Understanding of FND has developed dramatically in the last decade. Older conceptions of FND have been replaced by more nuanced biopsychosocial models that, whilst acknowledging the important role of stress, do not assume its relevance for all, 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’ which 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. Both patients gave written informed consent for publication.

**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 twenty minutes post-vaccination she developed an odd sensation (which the patient described as ‘weakness’) around the left ear which, over seconds, spread to the mouth and then to the left arm and leg over the rest of the day. There was no headache or other symptoms noted.

On waking the next morning, the patient had difficulty in moving the left side of her face as well as heaviness in her left leg. Her general practitioner (GP) called her an ambulance and the emergency department (ED) consultant and stroke team documented mild (4/5 on Medical Research Council power scale) left-sided arm weakness in the distal muscles and forearm, downwards 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 MRC 5/5 power was documented in the leg and no comment was made of any gait abnormality. She had normal blood pressure, glucose and heart rate, and an electrocardiogram and computed tomography scan of her brain were normal. She was discharged from ED with a working diagnosis of a transient ischaemic attack or Bell’s palsy and was started on aspirin 75mg once a day.

The left arm, leg, and facial weakness continued and peaked two days after the vaccine. When she was seen at the stroke clinic one-week later, she had ongoing left sided weakness on examination. The patient also reported a 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. A magnetic resonance imaging (MRI) brain scan at this clinic appointment, including diffusion weighted imaging (DWI), was normal. She was discharged from the clinic for follow-up in a general neurology clinic.

Two months post-vaccination, she was reviewed in a general neurology clinic (by JC). She had ongoing left sided weakness, particularly in grip strength, although weakness had gradually (albeit variably) improved over the preceding few weeks. She also reported ongoingdifficulties with her 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 signs.

Functional neurological disorder (FND) was diagnosed on the basis of positive neurological signs including Hoover’s sign, hip abduction test, and symptom variability. These 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 save a sore arm. Four weeks later, she received the second dose in her right arm and a few minutes after noted weakness in her right hand and new right leg limping which lasted for around two 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 right hand on the second day post-immunization. Additionally, she had exertional fatigue after walking short distances. After several days of these symptoms, she sought medical attention.

On examination, she was noted to have right upper extremity weakness and was not able to lift either leg in either sitting or supine positions. MRI of her 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 4+/5) in right upper and lower limbs, but normal reflexes and sensory exam.

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 MH & FS) seven 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, she demonstrated MRC 5/5 power in 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 complaining of rapid muscle fatigue, she was able to hold a one-pound weight for several minutes. She demonstrated a low amplitude rapid postural tremor in both hands with the appearance of an enhanced physiological tremor. Reflexes were normal. While walking she dragged her right foot with no arm swing on 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 describe two previously healthy people who developed probable FND after receiving a COVID-19 vaccine. FND is a common disorder which can lead to distressing and disabling symptoms which can resemble almost any form of neurological symptom; 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/or psychological stress can be relevant risks factors in the development of FND, however in many cases these are not, or are only a small part of the overall picture.15 FND is now instead diagnosed via the presence of positive neurological signs, for example Hoover’s sign. Clinician’s require experience in recognising 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 recognised that some acute responses to vaccinations mimic symptoms of allergic reaction or anaphylaxis, such as panic, collapse, and laryngeal dystonia that, do not have an immunological cause and are not directly related to the vaccine constituents.17Human papillomavirus vaccination (HPV) vaccinations in Brazil have precipitated functional seizures,18 and there were cases of FND following the H1N1 (Swine Flu) vaccination in Taiwan19 and South Korea.20 In both latter countries, these predominantly affected schoolchildren, and 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.21This phenomenon has been echoed in multiple other countries and in response to different vaccines.16,22Inappropriate management of these adverse events could be disruptive to vaccination programs, and vaccine providers should have training on recognising these disorders, which should be treated differently than, say, allergic reactions.

There is strong plausibility for the genesis of functional symptoms in response to vaccination which 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 symptoms or flu-like symptoms), as well as pain from the injection site, may trigger and/or evolve into functional symptoms.11,24

It is important that clinicians are able to recognise FND reactions to COVID-19 vaccines for two principal reasons:

1. First, patients may have less chance of improving with evidence-based treatment. This includes explanation of FND25 as well as demonstration of positive signs.26 The patient may also miss out on further multidisciplinary treatment for FND, where necessary.14
2. Second, that public perception of neurological adverse events to the vaccine are not damaged by misinformation which is easily spread by a globally interconnected social media. It is also more likely that patients may resort to other explanations at odds with scientific understanding, such as anti-vaccination theories, to explain their symptoms if they feel dismissed by clinicians.

Finally, this case highlights the importance of using positive signs, seen in these cases and in circulating videos on social media,9 to diagnose FND and distinguish from other neurological disorders. This is in contrast to current WHO recommendations advising that ISRRs are diagnoses of exclusion.13 We recommend that guidelines are 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 management14

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, and we consider FND to be the most likely explanation.

**Conclusions**

In these case reports two cases of FND were precipitated by administration of a SARS-CoV-2 vaccine. Our cases highlight that FND can be missed by clinicians but, is likely to arise in multiple cases within the large-scale SARS-CoV-2 vaccination programme. It is hoped that informing the public about the occurrence of FND, which is real and disabling, however which does not implicate any vaccine constituents, will help aid ongoing uptake in the SARS-CoV-2 vaccination programme.

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**References (max. 25)**

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15.

2. Holder J. Tracking Coronavirus Vaccinations Around the World [Internet]. New York Times. 2021 [cited 2021 Mar 29];Available from: https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html

3. European Medicines Agency. AstraZeneca’s COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets Share [Internet]. 2021 [cited 2021 Apr 8];Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

4. Wolfe RM, Sharp LK. Anti-vaccinationists past and present. Br Med J 2002;325(7361):430–2.

5. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403–16.

6. Facial Palsy UK Medical Advisory Board. Facial Palsy and Covid-19 vaccine [Internet]. [cited 2021 Feb 20];Available from: https://www.facialpalsy.org.uk/news/facial-palsy-and-covid-19-vaccine/

7. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. JAMA - J Am Med Assoc 2021;70(2):46–51.

8. Medicines & Healthcare Products Regulatory Agency. Coronavirus vaccine - weekly summary of Yellow Card reporting [Internet]. 2021 [cited 2021 Feb 22];Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

9. Functional Neurological Disorder Society. FNDS Press Release COVID Vaccines [Internet]. 2021 [cited 2021 Feb 20];Available from: https://www.fndsociety.org/UserFiles/file/FNDSSocietyPressReleaseCOVIDVaccines.pdf

10. Volpicelli G. They Claimed the Covid Vaccine Made Them Sick—and Went Viral [Internet]. Wired. 2021;Available from: https://www.wired.com/story/they-claimed-the-covid-vaccine-made-them-sick-and-went-viral/

11. Dongkyung D, Kung C, Perez D. Helping the Public Understand Adverse Events Associated With COVID-19 Vaccinations. JAMA Neurol 2021;

12. Stamelou M, Edwards MJ, Espay AJ, et al. Movement Disorders on YouTube — Caveat Spectator. N Engl J Med 2011;365(12):1160–1.

13. World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. World Health Organization; 2019.

14. Espay AJ, Aybek S, Carson A, et al. Current concepts in diagnosis and treatment of functional neurological disorders. JAMA Neurol [Internet] 2018;75(9):1132–41. Available from: https://doi.org/10.1001/jamaneurol.2018.1264

15. Keynejad RC, Frodl T, Kanaan R, Pariante C, Reuber M, Nicholson TR. Stress and functional neurological disorders: Mechanistic insights. J Neurol Neurosurg Psychiatry 2019;90(7):813–21.

16. Loharikar A, Suragh TA, MacDonald NE, et al. Anxiety-related adverse events following immunization (AEFI): A systematic review of published clusters of illness. Vaccine 2018;36(2):299–305.

17. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract 2021;

18. Marchetti RL, Gallucci-Neto J, Kurcgant D, et al. Immunization stress-related responses presenting as psychogenic non-epileptic seizures following HPV vaccination in Rio Branco, Brazil. Vaccine 2020;38(43):6714–20.

19. Lin CY, Peng CC, Liu HC, Chiu NC. Psychogenic movement disorder after H1N1 influenza vaccination. J Neuropsychiatry Clin Neurosci 2011;23(3).

20. Yang TU, Kim HJ, Lee YK, Park YJ. Psychogenic illness following vaccination: Exploratory study of mass vaccination against pandemic influenza A (H1N1) in 2009 in South Korea. Clin Exp Vaccine Res 2017;6(1):31–7.

21. Huang WT, Hsu CC, Lee PI, Chuang JH. Mass psychogenic illness in nationwide in-school vaccination for pandemic influenza A(H1N1) 2009, Taiwan, November 2009-January 2010. Eurosurveillance 2010;15(21).

22. Buttery JP, Madin S, Crawford NW, et al. Mass psychogenic response to human papillomavirus vaccination. Med J Aust 2008;189(5):261–2.

23. Stone J, Carson A, Aditya H, et al. The role of physical injury in motor and sensory conversion symptoms: A systematic and narrative review. J Psychosom Res 2009;66(5):383–90.

24. Butler M, Tamborska A, Wood G, et al. Defining Causality in Neurological & Neuropsychiatric Covid-19 Vaccine Complications: What Have We Learnt from Current and Previous Vaccination Campaigns? SSRN Electron J [Internet] 2021;Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract\_id=3823441

25. Stone J. Functional neurological disorders: The neurological assessment as treatment. Pract Neurol 2016;16(1):7–17.

26. Stone J, Edwards M. Trick or treat?: Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 2012;79(3):282–4.