

Functional neurological disorders after COVID-19 vaccination:

Case series and literature review

Letters to the Editor

A brief letter (734 words in the present paper, less than 750 words, excluding references; no abstract, and no key words. A total of 10 references or less. Up to 1 table or figure. 4 authors in the present paper, Maximum ten authors.) will be considered for publication. Novel case reports and other uncontrolled observations should be submitted as Letters to the Editor. Text should be unstructured and subheadings should not be used. Letters to the Editor can accompany supporting information.

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Running title: FND & COVID vaccination

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Dear sir,

Functional neurological disorder (FND) has been reported in individuals in isolation or as a part of a mass hysteria event, particularly in an adolescent cohort.^{1,2} The literature regarding FND after COVID-19 vaccination is quite limited³⁻⁷. Here we add the case details of the patients treated at our hospital who developed 'neuropathy-mimic' FND soon after receiving a COVID-19 vaccination.

This was a retrospective study at our hospital in Japan. We reviewed the digitized laboratory records of 199 patients examined in our hospital's neurophysiology division during the 6-month period from July 1 to December 31, 2021, all of whom were referred patients. All patients completed a standard nerve conduction study (NCS).¹⁰ Neuroimaging had been added when necessary. This retrospective-analysis study was approved by our hospital's Ethics Committee, and the requirement for informed patient consent was waived due to the retrospective nature of the study and the anonymization of the patients' information.

We identified seven patients with FND after their COVID-19 vaccination; they comprised 3.5% of all neurophysiology-referred patients (**Table 1**). They were six females and one male, mean age 36 years (range 20–57 years). All underwent COVID-19 vaccinations, and two had a history of mild organic adverse events. The mean interval between the vaccination and symptom onset was 1 day. All patients developed 'neuropathy mimic,' i.e., numbness and/or pain and weakness in the extremities. Other features were functional visceral disorder (n=3). Three of the patients had a tension-type headache, and three patients had a recent history of anxiety-depression. Positive signs suggesting FND, such as Hoover sign, abductor finger sign, etc., were carefully examined. All patients had normal NCS findings. Laboratory tests (including glucose,

hemoglobin A1C, and a urinalysis) were performed in all patients, and the results were normal. Neuroimaging tests were performed in the patients in whom a lesion in the proximal nerve or spinal cord was suspected, and the results were normal. Six patients were referred to the psychiatry clinic, which was beneficial for the patients, and the final diagnosis of FND was made.

The clinical manifestations of the seven patients are summarized as follows: young (mean age 36 years), female dominance (86%), and developing 'neuropathy-mimic' FND the day after receiving a COVID-19 vaccination. They also had functional visceral disorder and tension-type headache. Referral to the psychiatry clinic confirmed the diagnosis of FND, which was most likely due to anxiety-depression. These clinical features are mostly in accord with those of previously reported cases of vaccination-induced FND³⁻⁷ and general FND^{1,2} (**Table 1**). The present findings raise two clinical issues. The first is the mechanism of hypersensitivity. The patients reported having evoked/spontaneous numbness and/or pain. Hypersensitivity is a general feature in anxiety-depression patients,⁸ including their internal organs. Experimentally, water avoidance stress or painful electrical foot shock stress cause hypersensitivity.⁸ These sensory features might reflect biological changes in the FND brain, particularly in the amygdala, hippocampus, hypothalamus, prefrontal and insular cortex. Positron emission tomography (PET) studies revealed decreases in serotonin and GABA_{A/B} and an increase in CRF₁ in the above-described emotion-related area.⁸ A second issue is how to best manage patients with post-vaccination FND. Neurological complications of COVID-19 pneumonia are not common; the estimated rate is 0.005% (34/57,000).⁹ The most common neurological complication was altered mental status (57% of the cases,⁹ including delirium), followed by headache (14%), and immune-mediated neurological

diseases (e.g., Guillain-Barre syndrome, etc.). In contrast, severe neurological complications after covid-19 vaccine are a rare phenomenon.^{9,10} Predisposing factors were young age, female sex, pre-existing dementia, anxiety, and depression.⁹ These symptoms are real but not the direct result of toxic vaccine effects.¹⁰ Neurologists should thus take care to not miss true neurological diseases, but it is also necessary to properly diagnose patients with FND who need particular advice and care in the context of COVID-19 vaccination. Vaccine hesitancy, characterized by lack of confidence in vaccination and/or complacency about vaccination that may lead to delay or refusal of vaccination, might have undermined COVID-19 vaccination program.⁷ In fact, the WHO recently ranked vaccine hesitancy as one of the top 10 threats to global health.⁷ Clear recognition and appropriate management of FND will help combat vaccination hesitancy among a general population. In conclusion, we reported seven patients with 'neuropathy-mimic' FND after they received a COVID-19 vaccination. It is important to properly diagnose patients with FND who need particular advice and care in the context of COVID-19 vaccination.

Disclosure Statement

The authors declare no conflict of interest.

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Table 1. The clinical manifestations of the previously reported and present patients with FND after receiving a COVID-19 vaccination

authors	department	year	No. of cases	*age/sex	COVID-19 vaccine	organic adverse events of vaccination	interval between vaccination & symptom onset	chief manifestation of FND	other neuropsychiatric symptoms	laboratory investigations	interventions	outcomes
Ercoli et al.	neurology	2021	1	40s/M	unknown	not mentioned	same day	neuropathy-mimic: bilateral facial paralysis, left facial numbness, hypoesthesia		not mentioned	none	complete recovery
Butler et al.	neurology	2021	2	30s/F	Moderna (mRNA vaccine)	not mentioned	same day	neuropathy-mimic: weakness in right hand and leg, Hoover's sign positive; encephalopathy-mimic: disoriented to time, person, place, agitation, labile affect		not mentioned	none	complete recovery
				30s/F	PfizerBioNTech (mRNA vaccine)	not mentioned	same day	neuropathy-mimic: weakness in left-side face and arm, Hoover's sign positive		not mentioned	none	complete recovery
Sanjeev et al.	emergency unit	2022	2	20s/F	unknown	not mentioned	same day	myelopathy-mimic: leg weakness		laboratory test, nerve conduction study, lumbar MRI: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				40s/F	unknown	not mentioned	same day	encephalopathy-mimic: loss of consciousness, unresponsiveness		laboratory test, brain CT: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
de Souza et al.	neurology	2022	3	unknown	unknown	not mentioned	not mentioned	movement disorder -mimic		not mentioned	none	complete recovery
				unknown	unknown	not mentioned	not mentioned	movement disorder -mimic		not mentioned	none	complete recovery
				unknown	unknown	not mentioned	not mentioned	neuropathy-mimic: protracted limb weakness and sensory dysfunction (Guillain-Barre syndrome mimic)		not mentioned	none	complete recovery
Fasano et al.	neurology	2022	2	unknown	unknown	not mentioned	same day (20min after injection)	epilepsy-mimic: a short episode of generalized tonic-clonic seizures, followed by immobility of whole body		Electroencephalography: normal	none	complete recovery
				unknown	Astra-Zeneca vaccine	not mentioned	2 weeks	stroke -mimic: persistent dizziness and a subjective loss of tactile sensitivity in the right arm and leg.		Brain CT, electroencephalography: normal	none	complete recovery
Takahashi et al.	neurology	2022	7	20s/F	unknown	none	1 day	neuropathy-mimic: numbness and pain in the four extremities, left dominant, fatigue, weakness in the four extremities, gait difficulty		laboratory test, nerve conduction study: normal	none	complete recovery
				20s/M	Moderna (mRNA vaccine)	none	1 day	neuropathy-mimic: numbness and pain in the four extremities and face, fatigue, gait difficulty	functional visceral disorder: neurally mediated syncope, tension-type headache	laboratory test, nerve conduction study, brain MRI, cervical MRI: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				20s/F	unknown	subfever	1 day	neuropathy-mimic: numbness in the four extremities	anxiety-depression for the past 3 years, functional visceral disorder: irritable bowel syndrome-constipation type, neurally mediated syncope	laboratory test, cerebrospinal fluid exam, nerve conduction study, brain CT, abdominal CT: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				30s/F	Moderna (mRNA vaccine)	none	same day	neuropathy-mimic: numbness in the four extremities	anxiety-depression for the past 5 years, tension-type headache, functional visceral disorder: irritable bowel syndrome-constipation type, neurally mediated syncope	laboratory test, nerve conduction study, brain CT, cervical MRI: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				40s/F	PfizerBioNTech (mRNA vaccine)	none	7 days	neuropathy-mimic: numbness in the four extremities, left dominant	functional visceral disorder: globus hystericus (dysphagia)	laboratory test, nerve conduction study: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				40s/F	unknown	anaphylaxis mild, transient	same day	neuropathy-mimic: numbness in the four extremities	anxiety-depression for the past 4 years	laboratory test, nerve conduction study: normal	counseling & anxiolytics by psychiatric clinic	complete recovery
				50s/F	unknown	none	same day	difficult to speech, neuropathy-mimic: numbness in the four extremities, left dominant, fatigue, weakness		laboratory test, nerve conduction study, brain MRI, cervical MRI: normal	counseling & anxiolytics by psychiatric clinic	complete recovery

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Footnotes:

* age in decade for anonymity, CT: computed tomography, FND: functional neurological disorder,
MRI: magnetic resonance imaging

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