Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1 Study flow-chart

Table S1 General and obstetric characteristics of subjects before and during the COVID-19 pandemic

Table S2 Comparison of the EPDS scores for each item

Youji Takubo, MD, 1,2 Naohisa Tsujino, MD, PhD 3,12 Yuri Aikawa, MA, 2 Kazuyo Fukiya, MA, 3 Momoko Iwai, MA, 1 Takashi Uchino, MD, PhD 1,1 Megumu Ito, MD, PhD, 1,1 Yasuo Akiba, MD, 1,1 Masafumi Mizuno, MD, PhD 4,1 and Takahiro Nemo, MD, PhD 4,1

1Department of Neuropsychiatry, Toho University Graduate School of Medicine, Tokyo. Departments of 2Psychiatry, 3Obstetrics and Gynecology, Saiseikai Yokohamashi Tobu Hospital, Yokohama, and 4Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

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Functional neurological disorders after COVID-19 vaccination: Case series and literature review

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 coronavirus disease 2019 (COVID-19) vaccination is quite limited.3–7 Here, we add the case details of the patients treated at Toho University Hospital, Sakurai, Japan, 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 1 July to 31 December 2021, all of whom were referred patients. All patients completed a standard nerve conduction study.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 women and one man, 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’, that is, 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 and so on, were carefully examined. All patients had normal nerve conduction study findings. Laboratory tests (including glucose, hemoglobin A1C and a urinalysis) were carried out in all patients, and the results were normal. Neuroimaging tests were carried out 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 FND3–7 (Table 1). The present findings raise two critical issues. The first issue is the mechanism of hypersensitivity. The patients reported having evoked/spontaneous numbness and/or pain. Hypersensitivity is a general feature of functional neurological disorder.
| Authors                     | Department | Year | No. of cases | Age/sex | COVID-19 vaccine | Organic adverse events of vaccination | Interval between vaccination and 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                                      | Neuroptathy-mimic: bilateral facial paralysis, left facial numbness, hypesthesia                           | Not mentioned                                                      | Laboratory test, nerve conduction study                     | Counseling & anxiolytics by psychiatric clinic               | Complete recovery |
| Butler et al.               | Neurology  | 2021 | 2            | 30s/F   | Moderna (mRNA vaccine) | Not mentioned                        | Same day                                      | Neuroptathy-mimic: weakness in right hand and leg, Hoover's sign positive, encephalopathy-mimic: disorientation to time, person, place, agitation, labile affect | Not mentioned                                                      | Laboratory test, brain CT: normal                           | Counseling & anxiolytics by psychiatric clinic               | Complete recovery |
| Sanjeev et al.              | Emergency unit | 2022 | 2            | 20s/M   | Unknown         | Not mentioned                        | Same day                                      | Myelopathy-mimic: leg weakness                                                               | Laboratory test, nerve conduction study, lumbar MRI: normal         | 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: Persistent distance and a subjective loss of tactile sensitivity in the right arm and leg | Laboratory test, nerve conduction study                         | Laboratory test, brain CT: normal                           | Counseling & anxiolytics by psychiatric clinic               | Complete recovery |
| Fasano et al.               | Neurology  | 2022 | 2            | Unknown | Unknown         | Not mentioned                        | same day (12hrs after injection)             | Epilepsy-mimic: a short episode of generalized tonic-clonic seizures, followed by immobility of whole body | Electroencephalography: normal                                  | None                                                         | Complete recovery |
| Takahashi et al.            | Neurology  | 2022 | 7            | 20s/M   | Unknown         | None                                | 1 day                                          | Neuroptathy-mimic: numbness and pain in the four extremities, left foot, fatigue, weakness in the four extremities, gait difficulty | Laboratory test, nerve conduction study: normal                  | None                                                         | Complete recovery |
|                             |            |      |              |         | Unknown         |          |                                 | Ankle reflex negative, bilateral sensory loss, bilateral hypesthesia                             | Brain CT, electroencephalography: normal                             | None                                                         | Complete recovery |
|                             |            |      |              |         | Moderna (mRNA vaccine) |         |                                 | Anxiety-depression for the past 3 years, 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 |
|                             |            |      |              |         | Unknown         |          |                                 | Anxiety-depression for the past 4 years, 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 |
|                             |            |      |              |         | Moderna (mRNA vaccine) |         |                                 | Anxiety-depression for the past 5 years, 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 |
|                             |            |      |              |         | Moderna (mRNA vaccine) |         |                                 | Anxiety-depression for the past 5 years, 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 |
|                             |            |      |              |         | Moderna (mRNA vaccine) |         |                                 | Anxiety-depression for the past 4 years, 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 |
|                             |            |      |              |         | Moderna (mRNA vaccine) |         |                                 | Anxiety-depression for the past 4 years, 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 |

Table 1. Clinical manifestations of the previously reported and present patients with functional neurological disorder after receiving a coronavirus disease 2019 vaccination

†Age in decade for anonymity. CT, computed tomography; F, female; FND, functional neurological disorder; M, male; MRI, magnetic resonance imaging.
in anxiety-depression patients, including their internal organs. Experi-
mentally, water avoidance stress or painful electrical foot shock stress cause hypersensitivity. These sensory features might reflect biological changes in the FND brain, particularly in the amygdala, hippocampus, hypothalamus, prefrontal and insular cortex. Positron emission tomography studies showed decreases in serotonin and gamma-aminobutyric acid (GABA) and an increase in corticotropin-releasing factor type 1 in the above-described emotion-related area. The 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). The most common neurological complication was altered mental status (57% of the cases, including delirium), followed by headache (14%) and immune-mediated neurological diseases (e.g. Guillain–Barré syndrome, etc.). In contrast, severe neurological complications after COVID-19 vaccine are a rare phenomenon. Predisposing factors were young age, female sex, pre-existing dementia, anxiety and depression. These symptoms are real, but not the direct result of toxic vaccine effects. 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 could lead to delay or refusal of vaccination, might have undermined the COVID-19 vaccination program. In fact, the World Health Organization recently ranked vaccine hesitancy as one of the top 10 threats to global health. 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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Osamu Takahashi, BSc1, Ryuji Sakakibara, MD, PhD2
Setsu Sawai, MD, PhD3 and Tsuyoshi Ogata, MSc4
1Clinical Physiology Unit, Sakura Medical Center, and 2Neurology, Sakura Medical Center, Toho University, Sakura, Japan.
Email: sakakibara@sakura.med.toho-u.ac.jp
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Prospective clinical intervention study of aripiprazole and risperidone in the management of postoperative delirium in elderly patients after cardiovascular surgery

Delirium, which is a common neuropsychiatric syndrome characterized by acute changes in cognition, altered consciousness, and impaired attention, is associated with increased morbidity and mortality, cognitive dysfunction, prolonged hospitalization, and decreased quality of life. Recent reviews and meta-analyses have reported that second-generation antipsychotics (SGAs) are beneficial for the management of delirium with regard to efficacy and safety compared to haloperidol. Aripiprazole (ARP), one of the SGAs, has a unique pharmacological mechanism as a dopamine system stabilizer. ARP is a high affinity antagonist at the 5-HT2A receptor, which reduces extrapyramidal symptoms (EPS). Furthermore, ARP has been categorized as an agent with no risk of arrhythmia. Considering the risk factors for cardiovascular disease, ARP could be suitable for the management of postoperative delirium after cardiovascular surgery; however, to our knowledge, there is no literature regarding the usefulness of ARP for delirium in cardiac patients. Here, we performed a 7-day, prospective, clinical intervention study of ARP and risperidone (RIS) in the management of delirium to investigate the efficacy and safety of them in the management of postoperative delirium in elderly patients after cardiovascular surgery. This study was conducted in accordance with the tenants of the Declaration of Helsinki and was approved by the ethics committee of Kumamoto University Hospital, Kumamoto, Japan. All patients gave informed consent, and their anonymity was preserved.

Of the 210 subjects enrolled in this prospective study, 196 underwent surgery, of which 31 developed postoperative delirium. All 31 patients were assigned to ARP or RIS groups in turn by sex, regardless of the severity of delirium. Among the 31 patients enrolled in this comparative intervention, one patient recovered without the use of SGAs and was excluded from the analysis. A total of 30 patients were assigned to sex-matched groups of ARP (n = 15) or RIS (n = 15), and each SGAs were used for all of them for the management of their delirium symptoms. There was no significant difference in other demographic and clinical characteristics at baseline between the two groups excepted for body mass index (BMI) (Fig. 1a).

The mean Delirium Rating Scale-Revised-98 (DRS-R-98) and Clinical Global Impression-Severity (CGI-S) scores at baseline, which showed the