Movement Disorders and SARS-CoV-2

Wilson K.W. Fung, MD,[1] Alfonso Fasano, MD, PhD,[1,2,3,4,*] and Conor Fearon, MB, PhD[1]

Introduction

As we have entered the third year of the coronavirus disease 2019 (COVID-19) pandemic, it has become increasingly difficult to summarize all aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and movement disorders. However, although the early literature on this topic was disparate and disorganized, more systematic compilation and review of these data in recent months has given a better sense of the impact of COVID-19 in movement disorders patients.[1,2] We review the association of SARS-CoV-2 with movement disorders and highlight some gaps and controversies within these broad topics. We, first, discuss the impact of the COVID-19 pandemic on movement disorders patients. We, then, discuss the emergence of movement disorders in the setting of SARS-CoV-2 infection. Finally, we discuss the notable surge in functional movement disorders, both in the setting of SARS-CoV-2 infection and following COVID-19 vaccination.

The Impact of the COVID-19 Pandemic on Movement Disorders: Controlling for Confounders

Although there is some sparse data on the impact of COVID-19 on patients with dystonia[3] and tic disorders,[4,5] the overwhelming majority of impact studies have been undertaken in Parkinson's disease (PD) cohorts. The heterogeneity of PD patients with respect to age, disease severity, and comorbidities means that prevalence and outcome data in PD patients who contract COVID-19 have been conflicting. The reported prevalence of COVID-19 in PD has ranged from 0.57% (equivalent to a non-PD control group)[6] to 25.6% (more than double that of a non-PD control group).[6,7] This discrepancy can be explained by the

fact that the lower reported prevalence was from an Italian phone survey study, whereas the higher reported prevalence calculated the seroprevalence of SARS-CoV-2 among asymptomatic PD patients during the third wave of COVID-19 in Iran. These vastly differing figures highlight the importance of considering the study methodology and population from which those data are reported. Three recent meta-analyses have estimated that the prevalence rate is 2% to 5%.[8–10] In these meta-analyses, however, obesity, pulmonary disease, diabetes mellitus, and immune-compromise were all associated with contracting COVID-19 in PD patients. This suggests that canonical COVID-19 risk factors could drive an observed increased prevalence in PD. Another systematic review demonstrated that prevalence varied according to geography (2.6% in Spain, 0.9% in the United States, and variable values in different regions of Italy, ranging from 7.1%–8.5% in Lombardy, 0.9% in Tuscany, and 0.6% in Piedmont and in the Bologna district).[11]

Similarly, reported mortality among PD patients who contract COVID-19 has been of great concern. However, studies to date have recorded a range of case fatalities from 5.2% to 100%.[12,13] Once again, systematic reviews and meta-analyses have helped to clarify risk, with mortality estimates among PD patients ranging from 12% to 25.1%.[6,9,10] One study found no significant differences between COVID-19 patients with PD and without PD (OR = 1.42; 95% CI = 0.26; 7.70; $P = 0.687$).[9] In many other studies, advanced age, severe or advanced disease, and comorbidities all played a significant role in mortality, suggesting that age and frailty may be the drivers of mortality in PD patients.[14–17] Again, the study methodology and the heterogeneity of PD suggest that pooled mortality rates do not capture the nuances of which PD patients are at risk from SARS-CoV-2 and why. Importantly, however, in those PD patients who recover from COVID-19, there appears to be a very high proportion (up to 85%) who experience long-term negative sequelae within the spectrum of the so-called "long COVID", including worsening of motor function (51%), increased levodopa requirements

[1]Division of Neurology, Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital – UHN, University of Toronto, Toronto, Ontario, Canada; [2]Krembil Research Institute, Toronto, Ontario, Canada; [3]Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada; [4]Department of Parkinson's Disease and Movement Disorders Rehabilitation, 'Moriggia-Pelascini' Hospital – Gravedona ed Uniti, Como, Italy

*Correspondence to: Prof. Alfonso Fasano, Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, 399 Bathurst St, 7McL410, Toronto, Ontario, M5T 2S8 Canada; E-mail: alfonso.fasano@uhn.ca

(48.2%), fatigue (40.7%), brain-fog and other cognitive issues (22.2%), and sleep disturbance (22.2%).[18]

When considering the impact the COVID-19 pandemic has had on PD, one cannot ignore the detrimental effect of lockdowns/isolation on PD patients. This pandemic has highlighted the importance of physical exercise and social interaction on the well-being of PD patients. Motor and non-motor symptoms of PD worsen during lockdowns,[19] dyskinesia can worsen,[20] anxiety heightens,[21] impulsive-compulsive behaviors become more common,[22] sleep problems become more common,[23] and access to medications, physiotherapy, and exercise become more problematic.[24,25] Hence, the secondary effect of the COVID-19 pandemic on PD is more complex than the impact of SARS-CoV-2 infection alone.

Importantly, the current outcome data is almost entirely drawn from the pre-vaccination cohorts. Hence, proper re-evaluation of COVID-19 risk in vaccinated PD patients is urgently needed. Only one early population study from the United Kingdom indicates that PD may still increase the risk of poor outcome among vaccinated patients, but further studies are needed to understand the true risk.[26] In many ways, the difficulties we have had with assimilating data on PD in COVID-19 is not unique and implies a much broader difficulty with epidemiological studies of PD in general. Specifically, the heterogeneity and complexity of PD makes it difficult to perform rigorous studies without very large cohorts and careful consideration of confounders.

In summary, the COVID-19 pandemic is already demonstrating a significant negative effect on people with PD. Extracting how much of the direct impact is related to age, frailty, and comorbidities and what proportion of this effect is indirect (related to lockdown and isolation) has not been possible to date. The long-term effects of PD patients who have navigated this pandemic remains to be seen, but it is clearly going to have been detrimental.

The Emergence of Movement Disorders Following SARS-CoV-2 Infection: Causal or Coincidental?

There is a broad range of neurological manifestations of COVID-19. However, the new onset of a movement disorder in the setting of SARS-CoV-2 infection is rare with prevalence estimates across admitted COVID-19 patients of 0.2% to 1%.[27–29] The most common movement disorder seen is myoclonus (63.4% of movement disorder cases), ataxia (38.7%), oculomotor abnormalities (20.4%), action/postural tremor (10.8%), akinetic–rigid syndrome (5.38%), and more rarely catatonia, dystonia, and chorea (all in the range of 1%–3%).[30] Functional movement disorders (FMD) have been rarely reported so far

although the experience of our "COVID-19 clinic" seems to indicate a much higher prevalence, especially among vaccinated subjects.[31]

Myoclonus

COVID-19-associated myoclonus can be multifocal or generalized, positive or (more rarely) negative, proximal more than distal and can involve the face, tongue, larynx, trunk, and diaphragm. It is spontaneous or action-induced or can be stimulus-sensitive to touch and sound (usually when proximal). The onset is usually within 1 month of COVID-19 symptoms.[32] Most studies suggest a subcortical origin probably originating in the brainstem[33,34] although cortical spikes have rarely been demonstrated.[35,36]
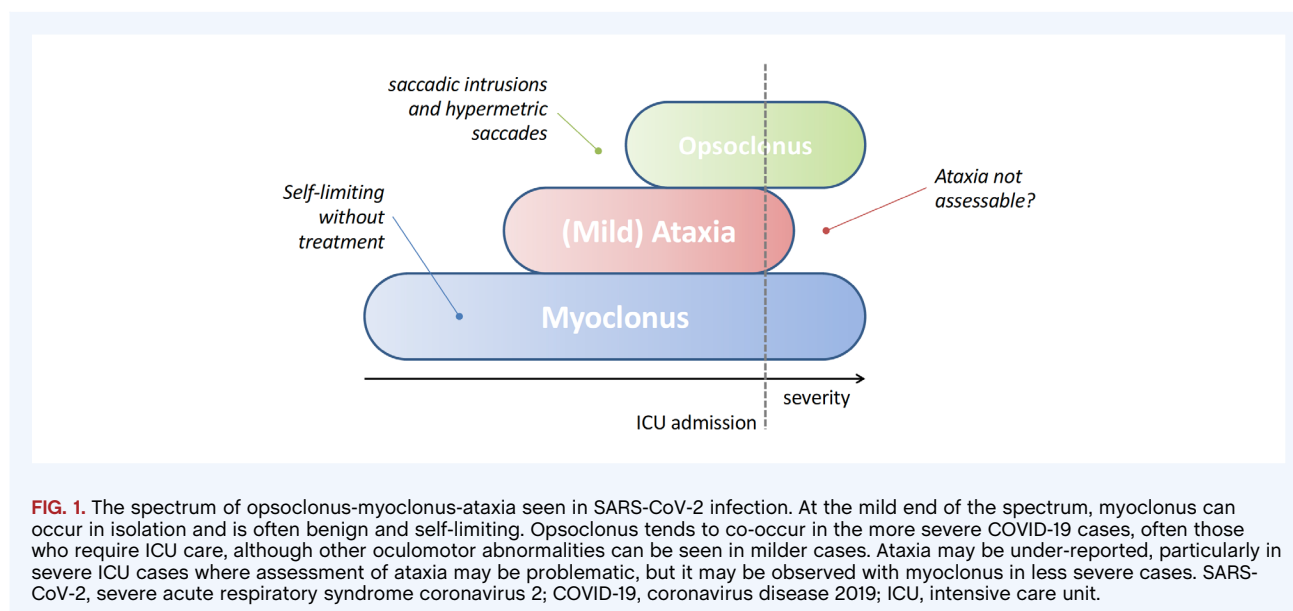
Ataxia

Although myoclonus has often been reported in isolation, it can frequently be accompanied by other signs. Ataxia, when present with myoclonus is usually mild and axial predominant.[37] Ataxia can however occur in isolation, either secondary to cerebellitis in children, which can be acute and severe (requiring surgical intervention)[38,39] or as a post-infectious process in adults where it runs a more benign immunoresponsive course.[40] Of course, ataxia can also occur for other reasons in COVID-19 including Miller Fisher syndrome,[41] Guillain-Barré syndrome,[42] myelitis,[43] anti-glutamic acid decarboxylase (GAD)-associated ataxia,[44] and mild encephalopathy with reversible splenial lesions (MERS).[45]

Oculomotor Disorders

Opsoclonus or ocular flutter has been reported in many patients with myoclonus and ataxia and these tend to occur in more severe cases suggesting that all of these cases form part of the opsoclonus–myoclonus–ataxia spectrum (Fig. 1).[33,46–51] These cases tend to have a benign prognosis, responding well to immunotherapy or resolving spontaneously.[52] Other oculomotor abnormalities including internuclear ophthalmoplegia, cranial nerve palsies, oscillopsia, ocular bobbing, and vertical supranuclear gaze palsy have all been described in the setting of SARS-CoV-2 infection.[53]

Tremor

Tremor has been reported in 13.8% of a series 165 COVID-19 patients at 6 months post-infection.[54] It tends to be a mild postural and action tremor and may be transient.[55] The etiology can include enhancement of physiological tremor (eg, because of medications or systemic conditions), cerebellar involvement, and fine distal jerks in the setting of neuropathy and functional tremor.[56]

FIG. 1. The spectrum of opsoclonus-myoclonus-ataxia seen in SARS-CoV-2 infection. At the mild end of the spectrum, myoclonus can occur in isolation and is often benign and self-limiting. Opsoclonus tends to co-occur in the more severe COVID-19 cases, often those who require ICU care, although other oculomotor abnormalities can be seen in milder cases. Ataxia may be under-reported, particularly in severe ICU cases where assessment of ataxia may be problematic, but it may be observed with myoclonus in less severe cases. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Chorea

Chorea is not uncommon in children, representing 3.9% of neurological complications of pediatric COVID-19 admissions in one study (0.15% of total cohort).[57] Two cases of Sydenham's chorea have been reported (one new-onset case and one relapse) in keeping with a possible autoimmune mechanism.[58,59] Chorea has been reported in adults (with striatal magnetic resonance imaging [MRI] abnormalities in some) although diabetes mellitus co-existed in at least two patients (presumed triggered by COVID-19 in one case).[60,61] Hence, chorea could also be an epiphenomenon of metabolic derangements in these patients.[2]

Parkinsonism

Since the beginning of the pandemic, particular interest has surrounded whether SARS-CoV-2 can cause parkinsonism. The theory that we might expect a significant increase in incidence of post-infectious parkinsonism as a result of SARS-CoV-2 was fueled by a number of factors.[62] The well-documented (but potentially unfounded) comparisons between post-encephalitic parkinsonism in the wake of the "Spanish" flu of 1914 to 1918,[63] the occurrence of anosmia in COVID-19 patients, and shared common pathophysiological mechanisms between dopamine synthesis and SARS-CoV-2[64] prompted many authors to suggest that a Parkinson's pandemic will follow. This concept was debated vigorously in the literature at the earliest stages of the pandemic.[65,66] As time progresses and numbers of infected individuals increase, it becomes increasingly apparent that true post-infectious parkinsonism is rare in COVID-19. We review the reported cases of parkinsonism in COVID-19 in Table 1. It is likely that a significant number of these represent unmasking of pre-existing subclinical PD. Acute emergence of parkinsonism during

stress may reflect pre-existing nigrostriatal damage, concealed in a pre-clinical phase via compensatory mechanisms. This nicely mirrors what was seen in behaviorally-normal rats with large dopamine-depleting brain lesions that became akinetic only when exposed to acute external stressors.[67] Based on the incidence of PD and documented global burden of SARS-CoV-2 infection, one would expect tens of thousands of newly diagnosed cases of PD among those infected over the age of 40. One of the more convincing post-infectious cases was of a previously healthy 58-year-old man who developed asymmetric tremor, rigidity, and bradykinesia following COVID-19.[68] He also demonstrated a fluctuating encephalopathy, distal myoclonus, episodic opsoclonus, and limited vertical gaze (with "round the houses" phenomenon). Dopamine transporter (DAT) SPECT imaging confirmed bilateral asymmetric decrease in presynaptic dopamine uptake involving both putamina. It appears that the atypical neurological features have now all resolved with the exception of typical asymmetric levodopa-responsive parkinsonism, suggesting that he may indeed have had underlying PD with a superimposed parainfectious opsoclonus-myoclonus-ataxia syndrome (personal correspondence with Méndez-Guerrero et al., 2020). Other mechanisms, such as silent hypoxemia, cytokine-related neuroinflammation, microglial activation, endothelial dysfunction, and megakaryocyte-mediated hemodynamic changes could contribute, as suggested by a case of severe parkinsonism following a prolonged ICU admission complicated by renal failure, refractory hypotension, and disseminated intravascular coagulation.[69] MRI brain demonstrated edema in the globus pallidus bilaterally and deep cerebellar nuclei containing small hemorrhagic foci with later atrophy of the globus pallidus and tissue loss in the dentate nuclei. A similar case with pallidal lesions but with levodopa-responsiveness has also been reported and silent hypoxia was the assumed culprit.[70]

TABLE 1 *Reported cases of parkinsonism in setting of SARS-CoV-2 infection including clinical and paraclinical features and likely etiology*

Reference	Age/sex	COVID-19 severity	COVID-19 to onset (days)	Atypical features	DA denervation	Brain MRI	Prodromal symptoms	Likely etiology
Cohen et al. 2020[71]	45/M	Admission	14–21		+ (typical)	Normal	No	Unmasking IPD
Faber et al. 2020[72]	35/	Mild	10	Slow saccades and gait impairment	+ (unilateral)		No	Unmasking IPD
Mendéz-Guerrero et al. 2020[68]	58/M	ICU	32	Decreased LOC, myoclonic jerks, opsoclonus, vertical gaze palsy	+ (typical)	Normal	No	Immune-mediated ± unmasking IPD
Akilli and Yosunkaya, 2021[73]	72/M	ICU	5	Encephalopathic, symmetric, reversible after convalescent plasma treatment and plasma exchange.	NA	Normal	No	Encephalitic? Akinetic-mutism
Makhoul and Jankovic 2021[74]	64/F	Mild	5		+ (unilateral)	Likely normal	Constipation	Unmasking IPD
Cavallieri et al., 2022[75]	67/M	Admission	120		+	Normal	No, GBA variant	Unmasking IPD
Cavallieri et al., 2022[75]	45/M	Mild	120		+	Normal	No, PRKN heter. variant	Unmasking IPD
Fearon et al., 2021[69]	46/M	ICU	91	Early axial involvement (hypophonia, freezing, instability), levodopa resistant, yawning, frontal lobe release signs	NA	Abnormal—pallidal and dentate lesions	No	Vascular/hypoxemic
Morassi et al., 2021[76]	70/F	Admission	77	Use of haloperidol, myoclonus, decreased LOC, seizure, ophthalmoparesis, limb fixed dystonia, rapid dementia	+	Progressive atrophy	Anxiety, depression	Encephalitic? Akinetic-mutism
Morassi et al., 2021[76]	73/F	Admission	0?	Treated with olanzapine and amisulpride, anarthria, vertical gaze palsy, decreased LOC, fatal outcome	NA	Traumatic hematoma	Anxiety, depression	Encephalitic? Akinetic-mutism

(Continues)

TABLE 1 Continued

Reference	Age/sex	COVID-19 severity	COVID-19 to onset (days)	Atypical features	DA denervation	Brain MRI	Prodromal symptoms	Likely etiology
Ayele et al., 2021[70]	35/F	ICU	?	Jaw-closing dystonia, drooling	NA	Abnormal – pallidal lesions	No	Vascular/hypoxemic
Ong et al., 2022[77]	31/M	Admission	6	Myorhythmia	NA	Abnormal – thalamic lesions	No	Encephalitic? Akinetic-mutism
Rao et al., 2022[78]	72/M	Admission	5	Early axial involvement (freezing, instability)	NA		No	Possible IPD, symptoms resolved with levodopa
Rao et al., 2022[78]	66/M	ICU	7	Immobile and mute	NA	Generalized atrophy, periventricular WM changes	No	Encephalitic? Akinetic-mutism
Rao et al., 2022[78]	74/M	Mild	56	Early axial involvement (instability)	NA	Periventricular WM changes	No	Unmasking IPD

Despite some animal models, which suggest that SARS-CoV-2 infection can lead to Lewy body formation in the absence of detectable viral RNA,[79] there is a paucity of evidence in human studies that COVID-19 can directly cause PD. Even in longer term follow up at 6 months, parkinsonism was present in only 0.46% of patients who had encephalopathy at time of infection.[80] Some of these cases may be an akinetic-mutism (that is well described in COVID-19 encephalitis) rather than true parkinsonism.[54,81] However, the potential for late increases in neurodegeneration among infected cohorts remains to be seen.

A Critical Review of Atypical Reports

A number of atypical cases have been reported that warrant mention. Two cases of diaphragmatic myoclonus/flutter, the etiology of which has been debated, have been reported.[82] Second, convergence spasm has been seen in a number of cases associated with either ocular flutter or opsoclonus.[33,83] Given that convergence spasm is most often of functional origin and that some of these cases have atypical findings, one must have a high degree of suspicion and critical appraisal of patients with these new onset movement disorders. As outlined in the next section, FMD following COVID-19 are not uncommon.

Given its time course and response to immunotherapy, almost all authors reporting cases of opsoclonus-myoclonus-ataxia syndrome postulate a parainfectious immune-mediated phenomenon. However, serum and cerebrospinal fluid (CSF) testing is usually normal.[33,84] Autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons have been reported.[85] Other antibodies reported in the setting of COVID-19 infection include LGI-1,[47] NMDAR,[86] CASPR-2,[87] MOG,[88] and GAD65.[44] We must consider the possibility that these antibodies are an epiphenomenon rather than directly causative, particularly when the clinical picture does not fit with the well-elucidated spectrum of those autoantibodies. Nevertheless, there is strong evidence to support an immune-mediated hypothesis, including the response to immunotherapy, self-reactive immune responses demonstrated in the central nervous system (CNS) of COVID-19 patients with neurological symptoms, and recently described candidate auto-epitopes (THAP3 and IFT88).[89] Other hypotheses for SARS-CoV-2-associated myoclonus include hypoxic injury,[90] direct viral CNS invasion,[91] cytokine-mediated inflammation,[34] adverse drug effects, or metabolic abnormalities[92] although it seems that these hypotheses lack convincing evidence or are rarer occurrences.

Hence, some movement disorders occurring acutely in the setting of COVID-19 are highly likely to be parainfectious, others may merely be unmasking of a pre-existing subclinical condition, and others (as we will discuss in the next section) are highly likely to be functional in origin.

Functional Movement Disorders and the COVID-19 Pandemic: A Potentially Greater and Underrecognized Problem

Reports of FMD in COVID-19 patients are increasingly common, although still likely to be under-reported.[31] With repeated restrictive measures in place across the world, changes in occupational status and reductions in social interactions, it is no surprise that there has been a significant amount of psychological distress experienced by many. One study reported a 2.3-fold increase in psychological distress in the first wave of the pandemic, with female sex and young age identified as risk factors.[93] There were initial concerns of deterioration in symptom control in FMD patients because of their increased susceptibility to stressful conditions, especially during the pandemic. However, several of these early studies found that the majority of patients did not report a clear change.[94–97] This included one case–control study in Italy.[97] The same group also found no worsening of FMD severity during repeated waves of COVID-19 infection.[98]

Over time, however, an increasing number of FMD cases have since been described, which has helped elucidate the spectrum of functional manifestations and their impact on clinical services. One single-center study demonstrated a 60.1% increase in new patients diagnosed with FMD during the pandemic.[99] The most common FMDs presenting to their clinic were hyperkinetic disorders, including tremor (53.3%), followed by dystonia (31.1%), myoclonus (17.8%), tics (8.9%), and stereotypy (8.9%). In 20% of cases, multiple types of FMD co-existed.

Tic-like behaviors in children and adolescents have also generated a lot of interest recently.[100,101] In many cases, these were functional tic-like behaviors, and there has been growing concern that social media, such as TikTok, has been fueling this pandemic.[102] A recent study found that 18.2% of new patients presenting with functional tics had preceding exposure to tic-like content on social media.[103] Similar to another study, all of these cases were young female patients with a phenomenology different to classic tics, namely more complex movements and an abrupt worsening when in the presence of others.[104]

Severe FMD cases resulting in hospitalization have also been reported. One study reported that 78.9% of their FMD patients required hospitalization because of symptom severity.[105] This included opisthotonic crises, dystonic features (43.3%), gait disorders including forced slowness, unsteadiness and cautious gait (41%), tremor (10.3%), functional tics, and non-epileptic seizures (5.1%). These patients also tended to have co-existing past mental health history (41% of cases), including prior psychological trauma. Fifty-three percent of patients were unable to work because of symptom severity, leading to significant socioeconomic implications.[105]

Furthermore, a significant proportion of COVID-19 survivors develop neuropsychiatric manifestations (up to 43%), including affective or post-traumatic stress disorders.[106] Psychological distress is likely to affect sicker patients and this was more common in intensive care unit (ICU)-admitted patients (46.9%) compared to ward patients (23.5%).[107] One example is a 54-year-old man, who developed functional head movements 2 months following severe COVID-19 infection.[108] He had developed significant neuropsychiatric symptoms, including severe anxiety and depression, cognitive impairment, fatigue, frequent headaches, and sleeping difficulties, which persisted for 1 year.

With the development of effective COVID-19 vaccinations, we have started to see less severe COVID-19-related illnesses. New challenges have arisen, however, with increasing reports of neurological side effects, including functional ones. These can include non-epileptic seizures, unexplained hemi-body sensory loss and bilateral facial weakness.[109,110] As reported in other vaccination campaigns, an "immunization stress-related response" might play an important role.[111] It is important to delineate if the type of adverse reaction is because of the vaccine itself or a stress reaction in the setting of vaccine administration.[112] The blurring of these two very different types of reactions can lead to spreading of misinformation surrounding COVID-19 vaccination and drive vaccine hesitancy.[109]

It is, therefore, important for clinicians to continue sharing their clinical experiences during the pandemic to appreciate the full magnitude of COVID-19-related functional disorders, including FMD following vaccination. Given the high prevalence of neuropsychiatric symptoms, a multidisciplinary approach is clearly needed.

Conclusion

As our knowledge and experience of COVID-19 and movement disorders continues to grow, there is a real need to parse the relevant information to plan for care for these patients in the short-term (given ongoing infections) and the long-term. We need to be able to advise patients of their specific risk from SARS-CoV-2 in the short- and long-term. We also need to understand, which aspects of movement disorders are directly related to SARS-CoV-2 infection and, which aspects may be related to unmasking or lockdowns. Similarly, we need to understand the specific risk of SARS-CoV-2 in patients with movement disorders independent of confounding factors. Finally, in view of the increase in FMD occurring in the setting of infection and vaccination, a high degree of clinical suspicion is required in all new acute movement disorders for appropriate treatments and resource planning. Given the long-term neuropsychiatric effects of COVID-19, one might expect that a FMD pandemic is more likely than a parkinsonian one.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C.

Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

C.F.: 1B, 1C, 3A.

A.F.: 1A, 3B.

W.F.: 1B, 1C, 3A.

Disclosures

References

1. Fearon C, Fasano A. Parkinson's disease and the COVID-19 pandemic. *J Parkinsons Dis* 2021;11(2):431–444.

2. Schneider SA, Hennig A, Martino D. Relationship between COVID-19 and movement disorders: a narrative review. *Eur J Neurol* 2022;29 (4):1243–1253.

3. Delgado C, Pareés I, Kurtis MM. Patients' perspective of dystonia symptoms during the SARS-CoV-2 pandemic. *Mov Disord*. Published online May 11, 2021;36(7):1485–1486. https://doi.org/10.1002/mds.28645.

4. Conte G, Baglioni V, Valente F, Chiarotti F, Cardona F. Adverse mental health impact of the COVID-19 lockdown in individuals with Tourette syndrome in Italy: An online survey. *Front Psych* 2020;11: 583744.

5. Mataix-Cols D, Ringberg H, Fernández de la Cruz L. Perceived worsening of tics in adult patients with Tourette syndrome after the COVID-19 outbreak. *Mov Disord Clin Pract*. 2020;7(6):725–726.

6. Artusi CA, Romagnolo A, Imbalzano G, Marchet A, Zibetti M, Rizzone MG, Lopiano L. COVID-19 in Parkinson's disease: Report on prevalence and outcome. *Parkinsonism Relat Disord* 2020;80:7–9.

7. Salari M, Etemadifar M, Zali A, Medghalchi A, Tehrani Fateh S, Aminzade Z, Bagheri Moghaddam S. Seroprevalence of SARS-CoV-2 in Parkinson's disease patients: A case-control study. *Mov Disord* 2021; 36(4):794–795.

8. Chambergo-Michilot D, Barros-Sevillano S, Rivera-Torrejón O, De la Cruz-Ku GA, Custodio N. Factors associated with COVID-19 in people with Parkinson's disease: A systematic review and meta-analysis. *Eur J Neurol* 2021;28(10):3467–3477.

9. El-Qushayri AE, Ghozy S, Reda A, Kamel AMA, Abbas AS, Dmytriw AA. The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: a systematic review and meta-analysis. *Rev Med Virol* 2021;32:e2278.

10. Khoshnood RJ, Zali A, Tafreshinejad A, Ghajarzadeh M, Ebrahimi N, Safari S, Mirmosayyeb O. Parkinson's disease and COVID-19: A systematic review and meta-analysis. *Neurol Sci* 2021;43(2):775–783.. https://doi.org/10.1007/s10072-021-05756-4.

11. Artusi CA, Romagnolo A, Ledda C, et al. COVID-19 and Parkinson's disease: What do we know so far? *J Parkinsons Dis* 2021;11(2):445–454.

12. Kobylecki C, Jones T, Lim CK, Miller C, Thomson AM. Phenomenology and outcomes of In-patients with Parkinson's disease during the coronavirus disease 2019 pandemic. *Mov Disord* 2020;35(8):1295–1296.

13. Hainque E, Grabli D. Rapid worsening in Parkinson's disease may hide COVID-19 infection. *Parkinsonism Relat Disord* 2020;75:126–127.

14. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord* 2020;35(6):905–908.

15. Parihar R, Ferastraoaru V, Galanopoulou AS, Geyer HL, Kaufman DM. Outcome of hospitalized Parkinson's disease patients with and without COVID-19. *Mov Disord Clin Pract* 2021;8(6):859–867.

16. Salari M, Etemadifar M, Ashrafi F, Ommi D, Aminzade Z, Tehrani FS. Parkinson's disease patients may have higher rates of Covid-19 mortality in Iran. *Parkinsonism Relat Disord* 2021;89:90–92.

17. Fasano A, Cereda E, Barichella M, Cassani E, Ferri V, Zecchinelli AL, Pezzoli G. COVID-19 in Parkinson's disease patients living in Lombardy. *Italy Mov Disord* 2020;35:1089–1093.

18. Leta V, Rodríguez-Violante M, Abundes A, et al. Parkinson's disease and post–COVID-19 syndrome: The Parkinson's long-COVID Spectrum. *Mov Disord* 2021;36(6):1287–1289.

19. Fabbri M, Leung C, Baille G, et al. A French survey on the lockdown consequences of COVID-19 pandemic in Parkinson's disease. The ERCOPARK study. *Parkinsonism Relat Disord* 2021;89:128–133.

20. Gultekin M, Tufekcioglu Z. COVID-19 infection presented as severe dyskinesia in a patient with Parkinson's disease: a case with daily video recording. *Neurol Sci* 2022;43(5):2961–2963.

21. Shalash A, Roushdy T, Essam M, et al. Mental health, physical activity, and quality of life in Parkinson's disease during COVID-19 pandemic. *Mov Disord Off J Mov Disord Soc* 2020;35(7):1097–1099.

22. Yule E, Pickering JS, McBride J, Poliakoff E. People with Parkinson's report increased impulse control behaviours during the COVID-19 UK lockdown. *Parkinsonism Relat Disord* 2021;86:38–39.

23. Kumar N, Gupta R. Impact of COVID-19 pandemic on Parkinson's disease: A tale of fears and sorrows! *Ann Indian Acad Neurol* 2021;24(2): 121–123.

24. Cheong JLY, Goh ZHK, Marras C, Tanner CM, Kasten M, Noyce AJ, the Movement Disorders Society Epidemiology Study Group. The impact of COVID-19 on access to Parkinson's disease medication. *Mov Disord* 2020;35(12):2129–2133.

25. van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, Bloem BR. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: A double-blind, randomised controlled trial. *Lancet Neurol* 2019;18(11): 998–1008.

26. Hippisley-Cox J, Coupland CA, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: National prospective cohort study. *BMJ* 2021;374: n2244.

27. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology* 2020;95(8):e1060–e1070.

28. Xiong W, Mu J, Guo J, et al. New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology* 2020; 95:e1479–e1487.

29. Misra S, Kolappa K, Prasad M, et al. Frequency of neurologic manifestations in COVID-19: A systematic review and meta-analysis. *Neurology* 2021;97(23):e2269–e2281.

30. Brandão PRP, Grippe TC, Pereira DA, Munhoz RP, Cardoso F. New-onset movement disorders associated with COVID-19. *Tremor Hyperkinetic Mov N Y N* 2021;11:26.

31. Fung WKW, Sa'di Q, Katzberg H, et al. Functional Disorders as a Common Motor Manifestation of COVID-19 Infection or Vaccination [published online ahead of print, 2022 Nov 11]. *Eur J Neurol*. 2022; doi:10.1111/ene.15630.

32. Chan JL, Murphy KA, Sarna JR. Myoclonus and cerebellar ataxia associated with COVID-19: A case report and systematic review. *J Neurol* 2021;268(10):3517–3548.

33. Khoo A, McLoughlin B, Cheema S, et al. Postinfectious brainstem encephalitis associated with SARS-CoV-2. *J Neurol Neurosurg Psychiatry* 2020;91:1013–1014.

34. Muccioli L, Rondelli F, Ferri L, Rossini G, Cortelli P, Guarino M. Subcortical myoclonus in COVID-19: Comprehensive evaluation of a patient. *Mov Disord Clin Pract* 2020;7:971–973.

35. Beretta S, Stabile A, Balducci C, et al. COVID-19-associated immune-mediated encephalitis mimicking acute-onset Creutzfeldt-Jakob disease. *Ann Clin Transl Neurol* 2021;8(12):2314–2318.

36. Cunha P, Herlin B, Vassilev K, et al. Movement disorders as a new neurological clinical picture in severe SARS-CoV-2 infection. *Eur J Neurol* 2020;27:e88–e90.

37. Schellekens MMI, Bleeker-Rovers CP, Keurlings PAJ, Mummery CJ, Bloem BR. Reversible myoclonus-ataxia as a Postinfectious manifestation of COVID-19. *Mov Disord Clin Pract*. 2020;7(8):977–979.

38. Fadakar N, Ghaemmaghami S, Masoompour SM, et al. A first case of acute Cerebellitis associated with coronavirus disease (COVID-19): a case report and literature review. *Cerebellum Lond Engl* 2020;19(6):911–914.

39. Sharma S, Ruparelia J, Bhaskar S, Tiwari S, Nag VL, Panda S. Acute fulminant Cerebellitis in children with COVID-19 infection: A rare but treatable complication. *Pediatr Neurol* 2021;119:45–47.

40. Povlow A, Auerbach AJ. Acute cerebellar ataxia in COVID-19 infection: A case report. *J Emerg Med* 2021;60(1):73–76.

41. Li Z, Li X, Shen J, Chan MTV, Wu WKK. Miller fisher syndrome associated with COVID-19: An up-to-date systematic review. *Environ Sci Pollut Res Int* 2021;28(17):20939–20944.

42. Li X, Wang Y, Wang H, Wang Y. SARS-CoV-2-associated Guillain-Barré syndrome is a Para-infectious disease. *QJM Int J Med* 2021;114:625–635.

43. Mondal R, Deb S, Shome G, Ganguly U, Lahiri D, Benito-León J. COVID-19 and emerging spinal cord complications: A systematic review. *Mult Scler Relat Disord* 2021;51:102917.

44. Emekli AS, Parlak A, Göcen NY, Kürtüncü M. Anti-GAD associated post-infectious cerebellitis after COVID-19 infection. *Neurol Sci* 2021;42(10):3995–4002.

45. Hayashi M, Sahashi Y, Baba Y, Okura H, Shimohata T. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. *J Neurol Sci* 2020;415:116941.

46. Nelson JL, Blume GM, Bansal SK, Kaufman JR, Woods FR, Zhang X, Kattah JC. Postinfectious SARS-CoV-2 Opsoclonus-myoclonus-ataxia syndrome. *J Neuro-Ophthalmol* 2021;42:251–255.

47. Smyth D, Kyaw KM, Legister A, et al. Post-COVID-19 opsoclonus-myoclonus syndrome and encephalopathy associated with leucine-rich glioma-inactivated 1 (LGI-1) antibodies. *J Neurol Sci* 2021;430:119982.

48. Ishaq H, Durrani T, Umar Z, Khan N, McCombe P, Ul Haq MA. Post-COVID Opsoclonus myoclonus syndrome: A case report from Pakistan. *Front Neurol* 2021;12:672524.

49. Saha B, Saha S, Chong WH. 78-year-old woman with opsoclonus myoclonus ataxia syndrome secondary to COVID-19. *BMJ Case Rep* 2021;14(5):e243165.

50. Fernandes J, Puhlmann P. Opsoclonus myoclonus ataxia syndrome in severe acute respiratory syndrome coronavirus-2. *J Neurovirol* 2021;27(3):501–503.

51. Urrea-Mendoza E, Okafor K, Ravindran S, Absher J, Chaubal V, Revilla FJ. Opsoclonus-myoclonus-ataxia syndrome (OMAS) associated with SARS-CoV-2 infection: Post-infectious neurological complication with benign prognosis. *Tremor Hyperkinet Mov N Y N*. 2021;11:7.

52. Foucard C, San-Galli A, Tarrano C, Chaumont H, Lannuzel A, Roze E. Acute cerebellar ataxia and myoclonus with or without opsoclonus: A Para-infectious syndrome associated with COVID-19. *Eur J Neurol* 2021;28(10):3533–3536.

53. Gold DM, Galetta SL. Neuro-ophthalmologic complications of coronavirus disease 2019 (COVID-19). *Neurosci Lett* 2021;742:135531.

54. Pilotto A, Cristillo V, Cotti Piccinelli S, et al. Long-term neurological manifestations of COVID-19: Prevalence and predictive factors. *Neurol Sci* 2021;42(12):4903–4907.

55. Klein S, Davis F, Berman A, Koti S, D'Angelo J, Kwon N. A case report of coronavirus disease 2019 presenting with tremors and gait disturbance. *Clin Pract Cases Emerg Med* 2020;4(3):324–326.

56. Clark JR, Liotta EM, Reish NJ, et al. Abnormal movements in hospitalized COVID-19 patients: A case series. *J Neurol Sci* 2021;423:117377.

57. Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: A prospective national cohort study. *Lancet Child Adolesc Health* 2021;5(9):631–641.

58. DeVette CI, Ali CS, Hahn DW, DeLeon SD. Acute rheumatic fever in a COVID-19-positive pediatric patient. *Case Rep Pediatr* 2021;2021:6655330.

59. Yüksel MF, Yıldırım M, Bektaş Ö, Şahin S, Teber S. A sydenham chorea attack associated with COVID-19 infection. *Brain Behav Immun Health* 2021;13:100222.

60. Ghosh R, Dubey S, Roy D, Ray A, Pandit A, Ray BK, Benito-León J. Choreo-ballistic movements heralding COVID-19 induced diabetic ketoacidosis. *Diabetes Metab Syndr* 2021;15(3):913–917.

61. Cotta Ramusino M, Perini G, Corrao G, Farina L, Berzero G, Ceroni M, Costa A. Sars-Cov-2 in a patient with acute chorea: Innocent bystander or unexpected actor? *Mov Disord Clin Pract*. 2021;8(6):950–953.

62. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: At the crossroad between aging and neurodegeneration. *Mov Disord* 2020;35(5):716–720.

63. von Economo K. Die encephalitis lethargica. *Wien Klin Wochenschr* 1918;30:581–585.

64. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *J Med Virol* 2020;92(10):1743–1744.

65. Gonzalez-Latapi P, Fearon C, Fasano A, Lang AE. Parkinson's disease and COVID-19: do we need to be more patient? *Mov Disord* 2021;36(2):277.

66. Merello M, Bhatia KP, Obeso JA. SARS-CoV-2 and the risk of Parkinson's disease: facts and fantasy. *Lancet Neurol* 2021;20(2):94–95.

67. Snyder AM, Stricker EM, Zigmond MJ. Stress-induced neurological impairments in an animal model of parkinsonism. *Ann Neurol* 1985;18(5):544–551.

68. Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *Neurology* 2020;95:e2109–e2118.

69. Fearon C, Mikulis DJ, Lang AE. Parkinsonism as a sequela of SARS-CoV-2 infection: Pure hypoxic injury or additional COVID-19-related response. *Mov Disord*. Published online May 27 2021;36:1483–1484.

70. Ayele BA, Demissie H, Awraris M, et al. SARS-COV-2 induced parkinsonism: the first case from the sub-Saharan Africa. *Clin Park Relat Disord* 2021;5:100116.

71. Cohen ME, Eichel R, Steiner-Birmanns B, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. *Lancet Neurol*. 2020;19(10):804–805. doi:10.1016/S1474-4422(20)30305-7

72. Faber I, Brandão PRP, Menegatti F, de Carvalho Bispo DD, Maluf FB, Cardoso F. Coronavirus Disease 2019 and Parkinsonism: A Non-postencephalitic Case. *Mov Disord*. 2020;35(10):1721–1722. doi:10.1002/mds.28277

73. Akilli NB, Yosunkaya A. Part of the Covid19 puzzle: Acute parkinsonism. *Am J Emerg Med*. 2021;47:333.e1–333.e3. doi:10.1016/j.ajem.2021.02.050

74. Makhoul K, Jankovic J. Parkinson's disease after COVID-19. *J Neurol Sci*. 2021;422:117331. doi:10.1016/j.jns.2021.117331

75. Cavallieri F, Fioravanti V, Toschi G, et al. COVID-19 and Parkinson's disease: a casual association or a possible second hit in neurodegeneration?. *J Neurol*. 2022;269(1):59–61. doi:10.1007/s00415-021-10694-4

76. Morassi M, Palmerini F, Nici S, et al. SARS-CoV-2-related encephalitis with prominent parkinsonism: clinical and FDG-PET correlates in two patients. *J Neurol*. 2021;268(11):3980–3987. doi:10.1007/s00415-021-10560-3

77. Ong TL, Nor KM, Yusoff Y, Sapuan S. COVID-19 Associated Acute Necrotizing Encephalopathy Presenting as Parkinsonism and Myorhythmia. *J Mov Disord*. 2022;15(1):89–92. doi:10.14802/jmd.21063

78. Rao AR, Hidayathullah SM, Hegde K, Adhikari P. Parkinsonism: An emerging post COVID sequelae. *IDCases*. 2022;27:e01388. doi:10.1016/j.idcr.2022.e01388

79. Philippens IHCHM, Böszörményi KP, Wubben JAM, et al. Brain Inflammation and Intracellular α-Synuclein Aggregates in Macaques after SARS-CoV-2 Infection. *Viruses*. 2022;14(4):776. Published 2022 Apr 8. doi:10.3390/v14040776

80. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324(6):603–605.

81. Delorme C, Paccoud O, Kas A, et al. COVID-19-related encephalopathy: A case series with brain FDG-positron-emission tomography/computed tomography findings. *Eur J Neurol* 2020;27(12):2651–2657.

82. Borroni B, Gazzina S, Dono F, et al. Diaphragmatic myoclonus due to SARS-CoV-2 infection. *Neurol Sci* 2020;41(12):3471–3474.

83. Shah PB, Desai SD. Opsoclonus myoclonus ataxia syndrome in the setting of COVID-19 infection. *Neurology* 2021;96(1):33.

84. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology* 2020;95(6):e767–e772.

85. Grimaldi S, Lagarde S, Harle JR, Boucraut J, Guedj E. Autoimmune encephalitis concomitant with SARS-CoV-2 infection: Insight from 18F-FDG PET imaging and neuronal autoantibodies. *J Nucl Med* 2020; 61:1726–1729.

86. Panariello A, Bassetti R, Radice A, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report. *Brain Behav Immun* 2020;87:179–181.

87. Kilic MA, Yoruk Yildirim ZN, Oner A, et al. Pediatric LGI1 and CASPR2 autoimmunity associated with COVID 19: Morvan syndrome. *J Neurol* 2021;268(12):4492–4494.

88. Durovic E, Bien C, Bien CG, Isenmann S. MOG antibody-associated encephalitis secondary to Covid-19: Case report. *BMC Neurol* 2021;21 (1):414.

89. Song E, Bartley CM, Chow RD, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. *Cell Rep Med* 2021;2(5):100288.

90. Ros-Castelló V, Quereda C, López-Sendón J, Corral I. Post-hypoxic myoclonus after COVID-19 infection recovery. *Mov Disord Clin Pract.* 2020;7(8):983–984.

91. Anand P, Zakaria A, Benameur K, et al. Myoclonus in patients with coronavirus disease 2019: A multicenter case series. *Crit Care Med* 2020; 48:1664–1669.

92. Mas Serrano M, Pérez-Sánchez JR, Portela Sánchez S, et al. Serotonin syndrome in two COVID-19 patients treated with lopinavir/ritonavir. *J Neurol Sci* 2020;415:116944.

93. Lorant V, Smith P, Van den Broeck K, Nicaise P. Psychological distress associated with the COVID-19 pandemic and suppression measures during the first wave in Belgium. *BMC Psychiatry* 2021;21:112.

94. Delgado C, Pareés I, Jiménez-Huete A, Kurtis MM. Impact of the coronavirus disease 2019 pandemic on functional movement disorders: Lessons from a specialized clinic. *Mov Disord* 2020;35:1723–1724.

95. Kanaan RA, Chen G, Olver J. How has the COVID pandemic affected functional neurological disorder? A mixed-methods analysis. *Gen Hosp Psychiatry* 2021;69:129–130.

96. Nisticò V, Goeta D, Gambini O, Demartini B. The psychological impact of COVID-19 among a sample of Italian patients with functional neurological disorders: A preliminary study. *Parkinsonism Relat Disord* 2020;78:79–81.

97. Di Vico IA, Riello M, Marotta A, et al. The impact of lockdown on functional motor disorders patients during the first COVID-19 outbreak: Acase-control study. *Parkinsonism Relat Disord* 2021;93: 40–42.

98. Sandri A, Di Vico IA, Riello M, Marotta A, Tinazzi M. The impact of recurrent Covid-19 waves on patients with functional movement disorders: a follow-up study. *Clin Park Relat Disord.* 2022;6:100139.

99. Hull M, Parnes M, Jankovic J. Increased incidence of functional (psychogenic) movement disorders in children and adults amid the COVID-19 pandemic: a cross-sectional study. *Neurol Clin Pract* 2021;11 (5):e686–e690.

100. Pringsheim T, Ganos C, McGuire JF, et al. Rapid onset functional tic-like behaviors in young females during the COVID-19 pandemic. *Mov Disord* 2021;36(12):2707–2713.

101. Heyman I, Liang H, Hedderly T. COVID-19 related increase in childhood tics and tic-like attacks. *Arch Dis Child* 2021;106(5):420–421.

102. Paulus T, Bäumer T, Verrel J, et al. Pandemic tic-like behaviors following social media consumption. *Mov Disord* 2021;36(12):2932–2935.

103. Pringsheim T, Martino D. Rapid onset of functional tic-like behaviours in young adults during the COVID-19 pandemic. *Eur J Neurol* 2021; 28:3805–3808.

104. Hull M, Parnes M. Tics and TikTok: Functional tics spread through social media. *Mov Disord Clin Pract* 2021;8(8):1248–1252.

105. Machado M, Tarrano C, Mesrati F, Roze E, Vidailhet M, Aubignat M. Functional movement disorders during the COVID-19 pandemic: Back to Charcot's era at the Salpêtrière. *Mov Disord* 2022;37(2):432–434.

106. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *Lancet Psychiatry* 2020;7(10):875–882.

107. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;93(2):1013–1022.

108. Garg A, Goyal S, Comellas AP. Post-acute COVID-19 functional movement disorder. *SAGE Open Med Case Rep* 2021;9:2050313X211039377.

109. Fasano A, Daniele A. Functional disorders after COVID-19 vaccine fuel vaccination hesitancy. *J Neurol Neurosurg Psychiatry* 2022;93(3):339–340.

110. Ercoli T, Lutzoni L, Orofino G, Muroni A, Defazio G. Functional neurological disorder after COVID-19 vaccination. *Neurol Sci* 2021;42(10): 3989–3990.

111. *Immunization stress-related response. A Manual for Program Managers and Health Professionals to Prevent, Identify and Respond to Stressrelated Responses Following Immunization.* Geneva: World Health Organization; 2019.

112. Taylor S, Asmundson GJG. Immunization stress-related responses: Implications for vaccination hesitancy and vaccination processes during the COVID-19 pandemic. *J Anxiety Disord* 2021;84:102489.